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CONTENTS OF PREVIOUS NUMBERS

OCTOBER, 1923. NUMBER 4

Bacteriologic Observations on Acute Tonsillitis with Reference to Epidemiology and Susceptibility. Arthur L. Bloomfield, M.D., and Augustus R. Felty, M.D., Baltimore.

Electrocardiographic Changes Following Occlusion of the Left Coronary Artery. Fred M. Smith, M.D., Chicago.

Studies on the Rabbit's Heart. I. Effect of Strophanthin on the Size of the Normal and of the Abnormal Heart. G. F. Strong, M.D., Vancouver, B.C., and Burgess Gordon, M.D., Spokane, Wash.

Studies on the Rabbit's Heart. II. Effect of Vigorous Exercise on the Size of the Normal and the Abnormal Heart. Burgess Gordon, M.D., Spokane, Wash., and G. F. Strong, M.D., Vancouver, B.C.

Giardia Interstinalis Infection. Edward Heilander, M.D., New York.

Malignant Lymphoma (Hodgkin's Disease). A Radiographic Study. Lester R. Whitaker, M.D., Cambridge, Mass.

Gonorrheal Myocarditis. Frank M. Phifer, M.D., and N. K. Forster, M.D., Chicago.

Clinical and Roentgenologic Study of One Hundred and Five Cases of Syphilis with Reference to the Cardiovascular System. Edward Steinfeld, M.D.; George E. Pfahler, M.D., and Joseph V. Klauder, M.D., Philadelphia.

The Influenza Epidemic at Camp Devens in 1918: A Study of the Pathology of the Fatal Cases. S. Burt Wolbach, M.D., and Channing Frothingham, M.D., Boston.

Observations on Changes in the Size and Shape of Hearts During the Progress of Compensation. J. C. Friedman, M.D., and Sidney Strauss, M.D., Chicago.

Observations on the Influence of Pituitary Extract on the Metabolism in Diabetes Insipidus. James F. Weir, M.D., Rochester, Minn.

Gastroscopy in Thirty Cases of Gastric Neoplasm. R. Schindler, Munich, Germany.

NOVEMBER, 1923. NUMBER 5

General Relation Between Susceptibility and Physiologic Condition. C. M. Child, M.D., Chicago.

General Observations on the Dynamics of Ventricular Systole. I. Auricular Fibrillation. L. N. Katz, M.D., and H. S. Fell, M.D., Cleveland.

Lambliа (Giardia) Infection Associated with Cholecystitis. Report of a Case Treated with Neo-Arsphenamin. J. L. Kantor, M.D., New York.

A Study of the Basal and Nitrogenous Metabolism in a Case of Acute Leukemia During Roentgen-Ray Treatment. W. G. Lennox, M.D., and J. H. Means, M.D., Boston.

Melanuria Without Melanosarcoma: Report of a Case. J. P. Peters, M.D., New Haven, Conn.

The Value of the Electrocardiograph in Pneumonia. W. A. Bloedorn, M.D., and L. J. Roberts, M.D., Washington, D.C.

Gastric Ulcer and Achlorhydria. J. R. Bell, M.D., London, Eng.

Experimental Infectious Streptococcus Endocarditis and Its Arsenical Therapy (Sodium Cacodylate). J. A. Bargen, M.D., Chicago.

The Complications of Staphylococcus Focal Infections. Laird M. Morris, M.D., San Francisco.

A Contribution to the Biochemistry and Treatment of Chronic Nephrosis (Epstein). I. M. Rabinowitch, M.D., and M. C. C. Childs, M.D., Montreal, Canada.

A Study of the Blood Oxygen in Diabetes Mellitus. S. B. Grant, M.D., Boston.

Gastric Secretion in Response to Duodenal Feeding. A. L. Garbat, M.D., New York.

Digitalis Elimination. Harry Gold, M.D., New York.

Observations on the Effects of Insulin in the Treatment of Diabetes Mellitus. I. M. Rabinowitch, M.D., Montreal, Canada.

DECEMBER, 1923. NUMBER 6

The Importance of Our Knowledge of Thyroid Physiology in the Control of Thyroid Diseases. David Marine, M.D., New York.

Elective Localization in the Eye of Bacteria from Infected Teeth. Russell L. Haden, M.D., Kansas City, Mo.

Renal Injury Produced in Rabbits by Diets Containing Meat. L. H. Newburgh, M.D., and Sarah Clarkson, M.S., Ann Arbor, Mich.

Periarteritis Acuta Nodosa. W. Ophüls, San Francisco.

The Bacteriophage in the Treatment of Infections. Earl B. McKinley, M.D., Dallas, Texas.

The Urea Concentration Factor in the Estimation of Renal Efficiency. I. M. Rabinowitch, M.D., Montreal, Canada.

Subacute Bacterial Endocarditis Due to a Hemolytic Hemophilic Bacillus: Report of a Case. C. Philip Miller, M.D., and Arnold Branch, M.D., New York.

Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica). N. E. Brill, M.D., and N. Rosenthal, M.D., New York.

Blood Counts in Hodgkin's Disease: Report of a Case. Kenneth R. McAlpin, M.D., New York.

The Etiologic Relation of Achylia Gastrica to Combined Sclerosis of the Spinal Cord: The Relief of Symptoms Following Adequate Hydrochloric Acid Therapy. Douglas Vanderhoof, M.D., Richmond, Va.

Book Reviews.

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THE DIAGNOSIS AND PATHOLOGIC PHYSIOLOGY OF ARTERIOVENOUS ANEURYSM *

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CLEVELAND

When the systemic arteriovenous circulation is short-circuited by a fistulous communication of sufficient size, symptoms develop so closely simulating those of myocardial decompensation that it may be difficult to evaluate the part contributed to the circulatory defect by the arteriovenous communication. In fact, the increased burden on the heart due to short-circuiting the flow of blood may in time produce genuine myocardial decompensation. The difficulties of diagnosis are still further complicated by the need of determining whether the arteriovenous communication is the sole cause of circulatory symptoms or only a contributory factor in the presence of cardiac disease. Obviously, if all the symptoms are due to arteriovenous fistula, the proper treatment is to close the opening. If the fistula is only a factor of minor importance, the operative procedure may be contraindicated. In the first case we have to report, the cardiac symptoms were so pronounced that a large number of physicians and surgeons advised against surgical procedure, believing the arteriovenous fistula to be of minor importance and the cardiac disease to be the chief cause of the existing venous stasis, chylous ascites and edema.

We find nowhere in medical literature a discussion of the hydraulics of arterial blood flow in arteriovenous fistula, nor any attempt to differentiate between cardiac enlargement caused by arteriovenous openings and that caused by primary disease of the myocardium. These questions must be unequivocally answered before a patient can be given sound advice on the question of operation. When the fistula is in a location that is under digital control, as in a fistula between the femoral artery and vein, it is a perfectly simple matter to compress the artery and determine how the hydraulics of the circulation are affected by eliminating the fistula from the circulation. When, however, the fistula is beyond manual control, as in the root of the neck or intrathoracic or intra-abdominal, the problem of diagnosis becomes much more difficult.

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We shall first describe two patients with arteriovenous fistula in the femoral vessels. In one patient the leak could be readily shunted out by compression of the femoral artery at Poupart's ligament, but in the other case the patient had so much edema and so much pain that he could not tolerate digital pressure on the femoral vessels, nor would he tolerate a ligature about the thigh. This was probably the reason that so many physicians had failed to evaluate the fistula in this man's circulatory symptoms.

REPORTS OF CASES

CASE 1.—*History.*—A young man, aged *32*, who was admitted to the Lakeside Hospital on Nov. *29*, 1920, had received a rifle bullet through the right thigh at the lower end of Hunter's canal, two years and two months before, while serving in a mortar battery with the army in France. According to the patient's history, he had no fever or any evidence of infection of his wound. About two weeks before he got out of bed, which was about two and a half months after receiving the wound, he observed that his right thigh and leg were swollen and decidedly larger than the left. When walking on crutches, he stepped on the right foot of the wounded side and held his left foot off the ground on account of a superficial wound in the left knee received at the same time as the wound in the right thigh. He observed that he was short of breath and began to have signs of fulness in the abdomen. He was then put to bed again and on examination was found to have free fluid in the abdominal cavity. Two weeks later his abdomen was tapped to relieve the ascitic accumulation. Within the following two years the abdomen was tapped forty times for the relief of ascites.

Examination.—When the patient came to the hospital he was able to walk by the aid of a crutch and a cane. The abdomen was greatly distended, and his thorax, extremities and face were emaciated. He seemed to suffer more from exhaustion than from air hunger. Although his ability to get about was limited, he did not cough or exhibit the symptoms of a patient suffering from a high degree of stasis in the pulmonary circulation. Physical examination revealed the apex of the heart at the fifth intercostal space, two thirds of the way to the anterior axillary line from the left midclavicular line. The impulse of the right ventricle was strong, and there were a distinct systolic impulse and a diastolic impact over its conus arteriosus. There was not a clear differentiation between the areas of impulse, but the left ventricular impulse could be differentiated from the right. The precordial area of dulness did not extend beyond the right border of the sternum in the third and fourth interspace. During inspiration the inner half of the left costal margin was diminished in its lateral movement, but the inner portion of the right costal margin moved readily away from the median line. The outer parts of both costal margins moved symmetrically outward during inspiration. The external and internal jugular veins were distended and under considerable pressure. When he was lying with his hands at his side, a distinct centrifugal systolic pulse was visible in the veins of the hands, and the right hand had to be lifted at least 12 inches above the level of the heart before the veins collapsed. The liver was plainly palpable four finger-breadths below the costal margin in the right nipple line. There was a strong systolic pulsation of the liver, which was synchronous with the pulse in the carotid artery; it was so strong that after the ascitic fluid was removed the pulsation of the liver caused a lateral thrust of the ribs on the right side that dragged the entire thorax to the right. With each cardiac systole the lower right ribs were thrust so far in a lateral direction that the borders of the left ribs were drawn toward the right. The

femoral vein on the right side was greatly distended, and the same kind of systolic pulse was visible as in the jugular veins, bulbus venosus and liver. At the lower end of Hunter's canal there was a strong thrill, which was palpable from that position as far upward as Poupart's ligament. Over this entire distance there was a loud systolic murmur, but below the origin of the thrill on the right side there was no murmur audible and no palpable thrill. The pulse in the dorsalis pedis artery was not palpable on either foot, but the posterior tibial pulse on both sides was distinctly palpable. The right thigh and leg were edematous, and there was also slight edema of the left leg and ankle.

A 6 foot (182.8 cm.) roentgenogram of the heart showed a globular enlargement. The contour revealed an enlargement of the right ventricle as well as of the left, but showed no evidences of distention of the right auricle to the right of the sternum. When synchronous tracings of the pulse in the bulbus venosus and in the femoral vein of the right side were taken, there was no evidence of an auricular pulse. The pulse was purely systolic in time, and the jugular pulse preceded that of the femoral by one tenth second, so that so far as pulsation of the liver, jugular vein and femoral vein were concerned, the patient evidently had a tricuspid insufficiency and the venous pulsations might be cardiac in origin or might originate from the arteriovenous opening. There were several reasons, however, for believing that the cardiac involvement was secondary to the arteriovenous fistula, and that all the venous phenomena originated from the direct arterial communication and not from cardiac decompensation.

The first reason was that the right auricle was not enlarged. If the venous phenomena at the bulbus venosus and in the liver were secondary to tricuspid insufficiency, there must be an enlarged right auricle, and therefore the fact that there was no evidence of flattening of the subcardial diaphragm at the right of the median line gave rise to the suspicion that the right auricle was not enlarged. Percussion, the fluoroscope and the roentgenogram all confirmed this finding. Moreover, the contour of the heart indicated that the right and left ventricles were equally involved and that their enlargement was due to a common cause. That it could not be from a decompensated left ventricle was suggested by the fact that the patient had a lung capacity of 2,500 c.c. when his expected vital capacity was not above 3,500 c.c. Had all the venous stasis been in consequence of a decompensation of the left ventricle, he would have had pronounced lung rigidity with a great reduction in his vital capacity. Under such circumstances, we should have expected the vital capacity to be reduced to about 1,500 c.c. or even 1,200 c.c.

Operation and Course.—As above stated, the patient would not tolerate sufficient pressure over the region of the femoral artery to shut out the arteriovenous leak. So in anticipation of an operation we could prognosticate only on the basis of the physical examination; but these two points—lack of evidence of stasis in the pulmonary circulation and of ectasis of the right auricle—were sufficient for advising operative procedure. Up to this time surgery had not been advised because the patient was believed to have a primary cardiac disease; to substantiate this interpretation, a positive Wassermann reaction on the blood had finally been procured after four trials, and this test had determined his physicians not to operate but to have the patient treated for syphilitic myocarditis.

On Dec. 5, 1920, we removed 11 liters of ascitic fluid by paracentesis. The fluid was milky in appearance and did not clarify by centrifugation. There were only 135 cells per cubic millimeter, and the amount of albumin, although not quantitatively determined, was smaller than that usually found in pure transudates. Although the fluid did not clarify by contact with ether, Dr. Blankenhorn was able to recover fat in considerable amounts by extraction with petroleum ether in a reflux condenser, and further studies of this fluid, reported elsewhere

by Dr. Blankenhorn,[1] proved its turbidity to be caused by fat in a finely divided emulsion. On the day after the ascitic fluid was removed, the patient was operated on, and there was no reaccumulation.

On Dec. 6, 1920, Dr. Crile operated on the patient under local anesthesia with nitrous oxid in small amounts. The patient was conscious during most of the operation. The vein and artery at the site of the communication were freely opened. On the inner surface of the artery, in an area 4 by 2 cm., there were about ten small sinuses plainly visible. The collected area of the lumina of all these sinuses, which presented a sievelike appearance, was not in excess of the cross section of the artery. This sievelike area was not removed, but was separated from the neighboring structures by deep ligatures on all four sides.

Directly after the operation it was quite apparent that there had been no primary heart disease and that all the circulatory symptoms had been caused by the arteriovenous fistula. The character of the heart impulse was immediately changed. Although the area of precordial dulness was not lessened, the systolic impulse and diastolic impact over the conus arteriosus of the right ventricle were no longer perceptible. Only the apex impulse was palpable. The contact of the cardiac impulse with the anterior chest wall was diminished in its vigor. One gained the impression that the heart was less globular and the right ventricle smaller, although the location of the apex of the left ventricle was unchanged and the right border of the heart was still at the right sternal border. The large veins were no longer distended, and the centrifugal systolic venous pulse in the jugular vein was replaced by a presystolic centrifugal wave. The hepatic pulse ceased, and the lower border of the liver was slightly below the costal border in the right nipple line. Its consistency was somewhat in excess of normal, and its edge slightly rounded—not so sharp as in hepatic cirrhosis. The impression received from palpating the liver before and after the operation was that the great engorgement within the hepatic veins was allayed but that the edema of the liver persisted. However, within a few days after the operation the liver was no longer palpable, and its percussion boundaries were quite normal.

There were several preoperative and postoperative observations that were interesting. For instance, before the operation the minute volume flow through the right foot (the affected side) was 1.16 gm. per 100 c.c. of foot volume, as measured by Stewart's method, and through the left foot it was 3 gm. per 100 c.c.; but one month after the operation the same method gave an equal volume flow on the two sides, namely, 1.8 gm. per 100 c.c. of foot, which is within the normal limits. Before the operation there was marked retention of body fluids, only about half the intake of fluids being eliminated by the kidney, although the phthalein kidney test gave a normal result. The urine at this time contained a trace of albumin and a few hyaline and granular casts. After the operation there was no retention of body fluids, and the urine became normal. The vital capacity of the lungs also became normal, being increased from 2,500 to 3,500 c.c. This increase in pulmonary extensibility was more apparent than real. It was in all probability unchanged, for the patient's muscular vigor was so much improved by the closure of the arteriovenous fistula that this alone could account for the apparent increase in lung capacity.

Besides the modification in size of the heart and the disappearance of venous engorgement, the most striking and interesting change was in the character of the arterial pulse. Before the operation the pulse was monocrotic and had an extent and celerity in the anacrotus and catacrotus that were suggestive of aortic insufficiency. The arterial pressure measured: systolic, 115; diastolic, 65. After the operation the pulse had a smaller excursion and the pressure measured:

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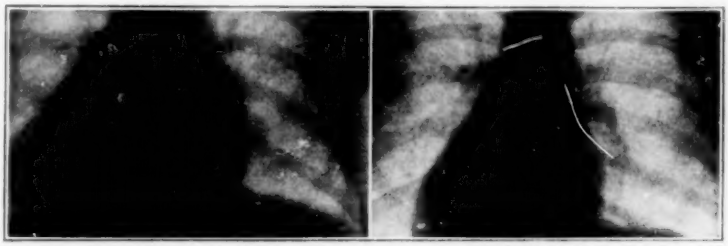
1. Blankenhorn, M. A.: Chylous and Pseudochylous Effusions: A Report of Seven Cases, Arch. Int. Med. **32**:129 (July) 1923. The Causes of Turbidity in Milky Ascitic Fluids, ibid., p. 140.

systolic, 145; diastolic, 95. This was a striking change in the systolic and diastolic pressure with the pulse pressure unchanged, and as we shall later show it occurs only in arteriovenous fistula. All other cardiovascular diseases that modify arterial pressures alter the pulse pressure.

By the latter part of February, eight weeks after the operation, the patient was discharged in perfect health. The roentgenograms of the heart taken before and after operation show a marked diminution in the size of the heart (Fig. 1, *A* and *B*). All the cardiovascular and respiratory signs were perfectly normal. The liver had a normal conformation, size and consistency. The urine was normal and the blood flow in the feet was the same.

Case 2.—*History.*—An Italian woman, aged 58, was admitted to Lakeside Hospital in April, 1921, complaining of shortness of breath and abdominal pain. Four years before entering the hospital she had been wounded by a rifle bullet in the upper right thigh. She was confined to her bed for eighteen days. After recovery from her wound she noticed a pulsation at the lower end of Scarpa's triangle. A year later there was dyspnea on slight exertion, and the ability to exercise grew gradually less.

Examination.—The patient had a well pronounced cardiovascular disease, as shown by the cardiac enlargement and an arterial pressure of: systolic, 210; diastolic, 110. In the jugular vein and bulbus venosus there was a systolic centrifugal pulse. The liver was at the level of the umbilicus in the mid-



A *B*

Fig. 1.—*A* is a 6 foot roentgenogram of Case I before operation; *B*, a 6 foot roentgenogram of the same patient one month after closure of the arteriovenous fistula.

clavicular line, and revealed a pronounced systolic pulse that was synchronous with that in the bulbus venosus. The contour of the heart was globular, although the differentiation between the areas of the left and the right ventricular impulses was more clearly defined than in the first patient. It was noticed, however, that although there was a pronounced hepatic pulse, the right boundary of precordial dulness did not extend beyond the right border of the sternum. The subcardial diaphragm was not flattened at the right of the median line, but it was depressed at the left, as shown by the inspiratory excursions of the costal borders. The inner half of the left border did not move outward during inspiration, but the outer half moved strongly laterad, as did the entire right costal margin.

There were no evidences of stasis in the pulmonary circulation. Four centimeters below Poupart's ligament there was an intense systolic thrill and loud systolic murmur, which was audible during the entire cardiac cycle, but which was greatly accentuated with the expulsive phase of the left ventricle. Although the femoral vein was enlarged, there was no edema of the thigh or leg of the affected side. When the femoral artery was obliterated at Poupart's ligament by digital compression, there followed some striking alterations in

the arterial pressure and character of the pulse. The systolic and diastolic blood pressures both rose 40 mm. of mercury, but the pulse pressure remained the same. Before compression of the femoral artery the pressure measured in either arm was: systolic, 210; diastolic, 110, and during compression it was: systolic, 250; diastolic, 150. When the arteriovenous leak was eliminated, the excursion of the radial and dorsalis pedis arteries was distinctly lessened, as perceived both by touch and by sight. With the arteriovenous leak, the pulse excursion had a range and celerity suggestive of insufficiency of the aortic valves or sclerosis of the aorta. When the arteriovenous leak was eliminated the pulse instantly assumed the character of pulsus durans, which is so marked in the Gull and Sutton variety of arterial sclerosis. The excursion of the artery was lessened, and an interruption high in the catacrotus was plainly visible and palpable in the dorsalis pedis, radial and brachial arteries. This alteration was clearly due to elimination of the systolic and diastolic leak from the femoral artery into the femoral vein. The systolic pulse in the jugular vein was replaced by a presystolic centrifugal pulse, which was plainly auricular in origin. The hepatic pulse ceased with elimination of the arteriovenous leak, and the size of the liver perceptibly diminished.

These changes in the arterial pulse are plainly shown in a tracing made from the radial artery, as seen in Figure 2. At *X*, the femoral artery above the

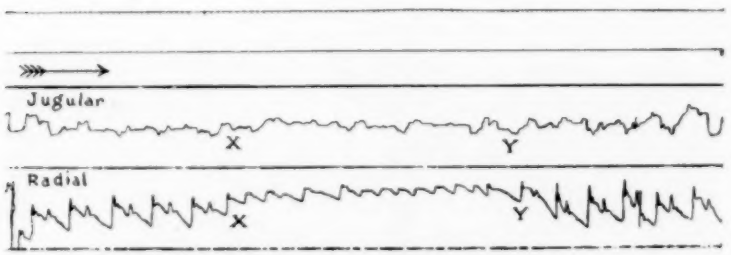


Fig. 2.—This tracing was made by the polysphygmograph from the jugular vein and radial artery of Case II. The running of the sphygmograph was not interrupted at any time in the tracing. The femoral artery above the arteriovenous fistula was compressed at the end of the diastole. Note the instant rise of the minimum diastolic descent with the recording needle. At *Y*, the artery was released, and immediately there was instant return to the original type of pulse.

fistula was compressed at the end of the cardiac diastole. Instantly the tracing rose to the same height as before compression, but the catacrotus descended only one third as far. The force of the spring that drove the pelote downward so as to register a downward excursion of the needle of 8 mm. now drove the needle downward only 3 mm. This was of course due to the increased filling of the artery and the rise of 40 mm. of mercury in the diastolic pressure. As the sphygmograph registers only the excursion of the arterial wall, with the stiffening of the arterial system the excursion of the wall is much diminished. At *Y*, the compression finger was lifted, and instantly the original arterial excursion was resumed. The pulse rate was distinctly increased when the leak was eliminated and not slowed as reported by other observers. The time marker shows no interruption in the tracing.

An operation was not advised in this patient because she had a severe cardiovascular and renal disease which forbade any promise of restoration to health after closure of the arteriovenous leak.

COMMENT

In the second patient the arteriovenous leak was not so large as in the first, but the hydraulics of the blood flow were affected exactly the same in both though in different degrees. In the second patient the significance of the arteriovenous leak was easily determined by compression of the femoral artery above the fistula.

In these two cases there are two demonstrable effects on the circulation that characterize the lesion and also enable the clinician to evaluate the burden added to the heart by the arterial leak. When there is a central leak, that is, of the aortic valves, the severity of the leak is clinically estimated by enlargement of the left ventricle and increase of the pulse pressure. If the diastolic pressure is lowered, there must be a compensatory rise of the systolic pressure to maintain a normal minute volume flow of blood. The left ventricle enlarges to accommodate a compensatory diastolic filling of its chamber. The leak, however, under these circumstances is purely diastolic. If there is a leak distal to the aortic valves, there will of necessity be an enlargement of all the chambers of the heart if the minute volume flow of blood is to be maintained. On the central side of the leak there must be an increased volume flow if the normal flow is maintained in all the distal parts. If 100 c.c. be the normal output of a left ventricle and an aortic diastolic leak of 20 c.c. be imposed, then the rate remaining the same, the systolic output of the ventricle must become 120 c.c., but only the left ventricle need enlarge to meet this compensatory measure. If the leak of 20 c.c. during the entire cardiac cycle occurs distally to the aortic valves, not only will there be required a compensatory dilatation of the left ventricle, but the right ventricle will have to meet an equal dilatation; an equal measure of dilatation on the part of the auricles, however, is for obvious reasons not required. The same kind of cardiac enlargement will be needed as occurs in other diseases attended with an increased minute volume flow through the heart. In acute exophthalmic goiter and severe chlorosis, the cavities of the ventricles enlarge, but the enlargement is compensatory; cardiectasis does not occur as in myocardial decompensation, and there is no demonstrable enlargement of the right auricle to the right of the sternum. Enlargement of the precordial area of dulness to the right of the sternum is always due either to ectasis of the right auricle or to an enlarged pericardial sac. The atrioventricular sulcus of the right side of the heart follows closely the right border of the sternum from the third to the fifth intercostal space. When the right ventricle enlarges, its base is not dislocated to the right, but its boundaries move upward to the left in the line of the conus arteriosus and laterally to it, and also downward to the left. When there is ectasis of the right

ventricle and auricle from myocardial decompensation, the subcardial diaphragm to the right of the median line is flattened, and the inner half of the right costal margin is restrained in its lateral movement during inspiration. In severe cases, it may be drawn mediad. When, however, the cardiac enlargement is compensatory for an increased volume flow of blood, as occurs in exophthalmic goiter or in arteriovenous fistula, the subcardial diaphragm is not flattened; the heart seems to be erect, and although enlarged it does not encroach on the phrenic arch.

The absence of enlargement of the right auricle is the most important sign in arteriovenous fistula when the volume of the leak is sufficient to cause a systolic liver pulse, for when an hepatic pulse is due to cardiac decompensation, the subcardial diaphragm at the right of the median line is flattened so that the inner half of the right costal border is either restrained in its laterad movement or drawn toward the median line in inspiration. This sign is the key to differential diagnosis when the leak is not under command of the fingers, for a globular enlargement of the heart, attended with a systolic centrifugal pulse in the veins and a strong hepatic pulse, is likely to be disposed of unquestioningly as venous stasis from cardiac decompensation. When the arteriovenous fistula is under digital command, it is an obvious and simple procedure to demonstrate the degree of arterial leak. If elimination of the leak does not modify the systolic and diastolic pressure, the arteriovenous fistula can have no significance for the systemic circulation. The change in blood pressure without change in the pulse pressure occurs only in this affection. All other sources of changes in blood pressure alter the pulse pressure. This is true in disease of the aortic valve and also when the output of the heart is increased or diminished if the peripheral resistance changes or remains the same.

Should a patient have arterial hypertonus with a pressure of systolic 250, diastolic 150, and the vasomotor tone be relaxed so that the systolic pressure is lowered to 210, the diastolic pressure will not be lowered an equal amount. The diastolic pressure may drop to 125 or 120, but it will not come down to 110, as occurred in our second patient when the arteriovenous leak was reopened after it had been eliminated by digital compression.

PATHOLOGIC PHYSIOLOGY OF ARTERIOVENOUS FISTULA

There were several considerations in these cases that demanded experimental confirmation and further clarification. The essential points we wished to study were: the changes in arterial pressure without change of pulse pressure; enlargement of both ventricles without ectasis of the auricles; and hepatic pulsation.

We soon found that anastomoses between normal vessels and fistulas between arteries and veins resulting from trauma gave different results. In neither of our two patients with femoral arteriovenous fistula could the leak have exceeded that of the cross section of a femoral artery, but the arterial and venous pressures were much more affected in our patients than in our experimental animals even when the proportionate arteriovenous anastomoses implicated a larger vascular lumen. In the first of our two patients, the arterial pressure was systolic 115, and diastolic 65 before the leak was closed and systolic 145, and diastolic 95 after the leak was closed; and in the second patient it was systolic 210 and diastolic 110 before and systolic 250 and diastolic 150 afterward. The soldier had a much larger leak than the woman, although his arterial pressure was raised 10 mm. of mercury less. The woman had severe arterial sclerosis, so that the stoppage of her smaller leak raised the pressure more than did the stoppage of the larger one in the man.

To reproduce these results in animals we anastomosed both carotid arteries of a dog with their adjacent external jugular veins, with the expectation that the consequent arteriovenous leak would proportionately equal or exceed that of our patients. With the aid of our surgical colleague, Dr. Frank Gibson, such anastomoses were made in May, 1922. By the middle of the following November, the dog showed no signs of venous stasis, and roentgenograms of the dog's heart made each month showed no appreciable alteration in the size of the heart. The dog was killed after an interval of six months, and the arteriovenous communications were perfectly clear, without obstructing thrombi in either vein or artery, and had a circumference of 7 mm. on each side. During life there were a strongly palpable thrill and a loud murmur over each opening, and if the lumina of the cut ends of the carotids had not been greatly diminished by vasomotor constriction, the circulatory changes in our first patient would have been reproduced, as the dog's arteriovenous communication at necropsy was proportionately much larger than our patient could possibly have had. We sought to remedy this constriction in the dog by dissecting off the adventitiae from the anastomosed arteries, but the thrombi in the veins at the points of anastomosis defeated the purpose of the experiment. When the dog's carotid-jugular anastomoses were freely opened, the character of the femoral pulse was perceptibly modified by alternately closing and releasing the carotids, but the palpable changes in the character of the pulse were not so pronounced as in either of the two patients with unilateral fistula in their femoral vessels.

We then tried anastomosing one common carotid artery of a dog with its neighboring external jugular vein so that the proximal end of the artery opened freely into the vein. An arteriovenous leak as

great as in either of the patients above described might have been expected, but the results were disappointing. After the carotid-jugular communication was established, the palpable thrill and murmur indicated a large leak, and by palpating the femoral artery while the arteriovenous opening was alternately closed and opened, the change in the character of the femoral pulse was plainly perceptible to the palpating finger. When the arteriovenous communication was open, the excursion of the femoral artery partook of the celer character, and when it was closed the artery had less excursion. When a cannula connected with a mercury manometer was inserted in the central end of the femoral artery, the changes in pressure were found to be considerably less than one would expect from the thrill and murmur and the palpable and

Fig. 3.—The tracing is from the femoral artery by means of a U mercury manometer. At *O*, the arteriovenous communication between the carotid and the external jugular was opened. At *S* it was closed. The changes in pressure recorded by this method do not reveal the points of opening and closure of the carotid-jugular path.

visible changes in the femoral arterial pulse. The arterial pressure from such an experiment is recorded in Figure 3. Although the femoral artery was fuller and the walls were more taut when the arteriovenous opening was closed, the pressure tracings fail to show when the opening was closed or open. The pressure changes were not sufficient to surmount those that occurred with respiration.

This experiment (with the one previously described, in which both carotids and jugulars were united) shows clearly that when arteriovenous communications are established between vessels with normal walls, the results are different from those that occur in arteriovenous fistula following trauma. In normal vessel walls the vasomotor defense

against hemorrhage is operative, whereas in diseased walls the leak is constant and unaffected by vascular constriction. Two arteriovenous communications, each found at necropsy to have a circumference of 7 mm., would in a 12 kilogram dog provide a proportionately much larger leak than a unilateral arteriovenous fistula in the femoral artery of man. In the experimental dog, however, we are dealing with the cut ends of normal arteries, which respond with vasomotor constriction as a defense against hemorrhage; but in wounded patients the arteriovenous fistulas are found in vascular walls that have lost their unstriped muscular fibers where the fistulas form.

CONFUSION WITH AORTIC INSUFFICIENCY

In several French publications during and since the war patients similar to our first one are described as having cardiovascular symptoms like those of insufficiency of the aortic valves. The authors describe the pulse as having a celer character quite like that of aortic insufficiency, and the heart is also described as having the size and contour seen in this valvular defect. According to our observations the size and contour of the heart and the pulse differ greatly in the two conditions. The size and contour of the heart will be reserved for later discussion, and for the present we will describe the pulse character and the arterial blood pressure.

Celerity of the pulse as described in the French publications is not celerity in arterial pressure variations but in extent of excursion of the arterial wall. As shown in our experiment in which only one carotid of a dog was connected with the jugular vein, the opening of the arteriovenous communication caused a visibly increased excursion of the exposed femoral artery, but the systolic and diastolic pressure failed to show when the arteriovenous communication was open or closed. By palpation the opening and closure of the arteriovenous communication could be accurately perceived, and still the mercury manometer was not sufficiently delicate to record the variations in pressure. In our second patient, who had arterial sclerosis, closure of the leak changed a pulsus celer into a pronounced pulsus durans, with a rise of 40 mm. of mercury in the maximum arterial pressure; but in spite of this marked visible and palpable transformation from pulsus celer to pulsus durans, the pulse pressure remained the same, as measured by the pneumatic cuff on the arm.

To obtain accurate data on the relation between pulse pressure and arteriovenous fistulas, we employed the Hürthle apparatus designed for the purpose, but our results were equivocal. The nature of the experiment was such that other factors than the A-V communication came into play, and the results gave both negatory and confirmatory

results, as one chose to measure the pulse pressure at selected intervals. The results were not as satisfactory as those obtained with the mercury manometer. So far as our endeavors are concerned, we are compelled to abide by the results of the pneumatic cuff, which gave the same results not only in our cases but in the cases of four other observers, who report the unchanging pulse pressure although the fact did not arouse their interest.

Whether the cuff is an absolutely correct method or not for measuring pulse pressure does not affect the value of the clinical observations. The fact remains that, with the best clinical method for the purpose, pulse pressure is found to be unchanged with alterations in maximum pressure in this lesion only. Furthermore, when closure of an A-V opening does not modify the systolic pressure, the lesion is of no serious significance for the circulation.

Figure 4 was made by a mercury manometer connected with the carotid artery of a dog in which the proximal ends of the cut abdominal aorta and cava were connected by a paraffined U-tube. At the points marked *S*, the A-V communication was shut, and at *O* it was opened. The tracing shows the systolic pressure much higher and the pulse pressure smaller during the shut periods. There is a difference of 25 mm. of mercury in pressure between the two periods, but the pulse pressures differ only by 4 mm. Furthermore, during the closed periods the pulse pressure recorded is the smaller, which differs from what happens when arterial pressure is raised by other means. Even by this recording method, as the pressure rises from the use of epinephrin the pulse pressure increases.

Although the mercury manometer does not accurately trace the pulse pressure, it betrays gross changes. This is shown in a carotid pressure tracing in an experiment of the same kind. At *S*, Figure 5, the A-V communication was closed, and at *O* it was open; then at *ad* the drum was stopped and 5 minims (0.3 c.c.) of 1:1,000 epinephrin were injected intravenously. With the A-V communication left open, the pressure rose from 90 to 130 mm. These pulse pressure changes are the reverse of those which occur when an A-V communication is opened and closed, as shown by the mercury manometer. Epinephrin raises the blood pressure and enlarges the pulse pressure; closing an A-V opening raises the arterial, but does not increase the pulse pressure. While the pulse pressure was enormously increased under the maximum effect of epinephrin, at *S'* the A-V opening was closed and at *O'* again opened. Of course here we have two operating factors, one a constant; that is, the opening and closure of the A-V communication—and the other a variant; that is, vasomotor pressor effect. But in the periods of *S'* and *O'*, where the pressor effect seems probably

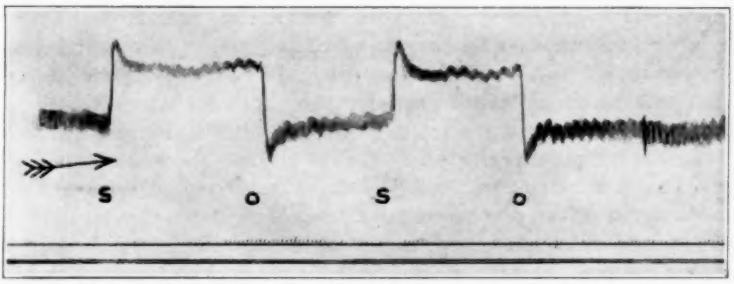


Fig. 4.—The tracing was made by a mercury U manometer connected with a carotid artery in a dog with the central ends of the cut aorta and cava connected by means of a paraffined U-tube. At *S* the aorta was closed. At *O* the aorta was released.

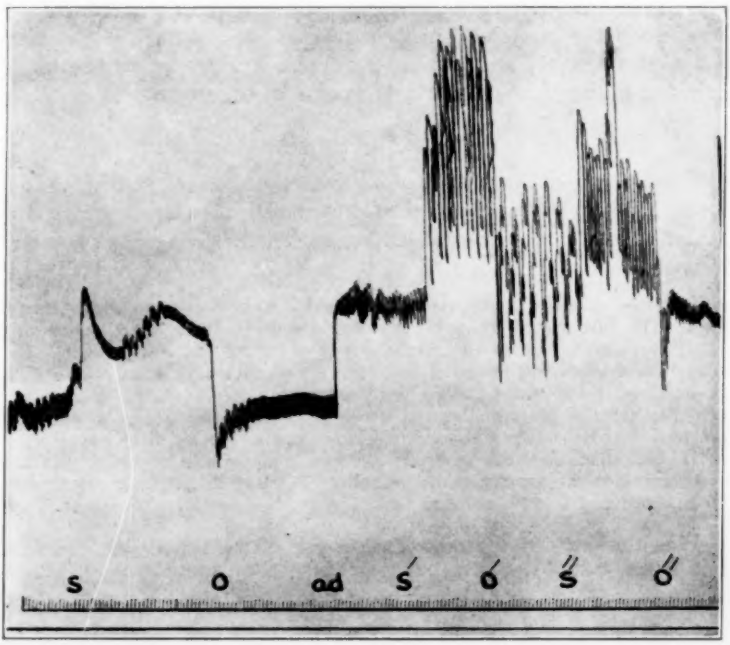


Fig. 5.—At *S* the communication between the aorta and cava was closed. At *O* it was opened. At *ad* the drum was stopped and epinephrin injected, followed by the prompt rise in pressure. At *S′* the arteriovenous opening was closed; at *O′* it was opened; at *S″* it was closed, and at *O″* it was opened.

the same, the pulse pressure is little changed at O' by opening the A-V passage, although the systolic pressure is much lowered by the procedure. Insufficiency of the aortic valves lowers the diastolic pressure and is attended with a compensatory rise in the systolic pressure. Every change in maximum blood pressure that occurs with any disease of the aortic valves or the aorta or peripheral arteries is attended with change in the pulse pressure.

The rise in maximum blood pressure of our second patient when the A-V communication was closed came promptly with the closure. When the femoral artery above the fistula was compressed at the end of a cardiac systole, the next arterial pulse apparently had the maximum rise, and this blood pressure and pulse pressure were maintained until the A-V communication was reopened, when the return to the former arterial and pulse pressure as promptly followed. This change is too prompt to include any vasomotor factor.

The mechanism of an arteriovenous leak differs from that of the central leak (aortic insufficiency) and of the peripheral leak (vasomotor relaxation). In the central leak the mechanism is operative during diastole and not in systole; in the arteriovenous leak and in the vasomotor relaxation the mechanism is operative during the entire cardiac cycle, but in the latter there is modification of the vascular capacity.

LESIONS SIMULATING ARTERIOVENOUS FISTULA

This absence of change in pulse pressure is not only pathognomonic of the lesion, but it also serves to differentiate between arteriovenous fistula and conditions that may simulate it. The following case illustrates this point:

CASE 3.—A healthy young man was wounded by a shot from an automatic pistol. The ball passed through the lower end of Hunter's canal. Over this area there was a painful swelling about 7 cm. long and 4 cm. wide. The region was sensitive to pressure, and over the swollen area there was a loud murmur during the entire cardiac cycle with accentuation during the systole. Over the same area there was a strongly palpable thrill, which was first perceived three days after the accident. There was no venous distention. When the femoral artery on the affected side was compressed, the blood pressure as measured in the arm remained systolic, 110; diastolic, 70, but the cardiac rate was reduced from 72 to 56.

Was this an arteriovenous aneurysm? It was not. In the first place, the prompt appearance of the palpable thrill after the accident proved that there would be no arteriovenous fistula. As seen in all our cases, about two weeks are required after the occurrence of a wound before a fistula forms. In the second place, the blood pressure was not changed by compression of the femoral artery. There was, it is true, marked slowing of the pulse, which has been repeatedly stated in medical literature to be a sign of arteriovenous fistula, but the slowing

of the heart rate seems to be caused by some afferent nerve impulse that is released when the wounded artery is compressed, and cannot be linked with any effect on the hydraulics of blood flow.

At operation there proved to be no arteriovenous communication in this case. The artery and vein were completely severed, and all four ends of the two vessels lay free within a blood sac. The free ends of the vein evidently acted as clapper valves and thus prevented blood from entering either the proximal or distal end. The free distal end of the artery, however, had so much resistance in its wall that the lumen remained partly open and thus admitted sufficient affluent blood so that the pulses in the dorsalis pedis and posterior tibial of the affected side were plainly palpable.

SIZE OF THE HEART

The size and contour of the heart are important, and a clear exposition of both may lead to a correct diagnosis when the arteriovenous fistula cannot be eliminated by arterial compression on account of pain or inaccessibility. In our first case, the fistula was accessible, but it could not be eliminated on account of extreme tenderness to pressure in Scarpa's triangle. The patient's heart was enlarged, as shown by the palpable impulse and dulness to the left of the midclavicular line. The area and force of the cardiac contact with the anterior thoracic wall were much increased, as shown by the broad quadrilateral impulse that was plainly palpable over the entire anterior area of the right ventricle. In spite of the enlarged heart, high venous pressure and great hepatic pulse, we were skeptical that myocardial incompetence was a causative factor, because there were no evidences of stasis in the pulmonary vessels, and the precordial area of dulness did not extend to the right of the sternum, nor was there any evidence of flattening of the subcardial diaphragm to the right of the median line. Because there was much enlargement of the ventricles and no evidence of pulmonary stasis or enlargement of the right auricle, we advised operation. Immediately after the operation the broad area of cardiac impulse over the right ventricle ceased. The contact of the right ventricle with the chest wall was much less vigorous, but the precordial area of dulness was unchanged until two weeks after the operation, when the heart returned to its normal size.

The following case well illustrates the need of interpreting the size and contour of the heart when the arteriovenous fistula is beyond digital control:

CASE 4.—The patient was seen by one of us (C. F. H.) a month before the first patient described in this paper came under observation. (It was not until the second experience that the former case could be satisfactorily interpreted.) A young man, aged 25, two months before was struck with great violence just above the right sternoclavicular joint by the handle of a mop. There was no

wound of the skin and no immediate results to indicate that there had been a serious injury. Two weeks later the patient suddenly developed a sense of extreme fulness and oppression over the upper thorax, which was caused by the establishment of a communication between the carotid artery and the jugular vein close to the innominate vessels. The jugular vein and bulbus venosus were greatly distended and pulsated violently and synchronously with the arterial pulse. The liver was four fingerbreadths below the costal margin in the nipple line and showed a strong systolic pulsation. The impulse of the left and right ventricles was greatly increased in intensity, and the area of the heart extended to the left midway between the nipple and anterior axillary lines. The area of heart dulness did not extend to the right of the sternum in the third, fourth and fifth interspaces, but there was an area of dulness like a band about 2 cm. wide to the right of the manubrium from the first to the third ribs.

With this combination of cardiac enlargement, venous engorgement and hepatic pulsation there was no evidence of pulmonary rigidity or edema, and there was no evidence of flattening of the subcardial diaphragm to the right of the median line. The entire right costal margin moved laterad in inspiration.

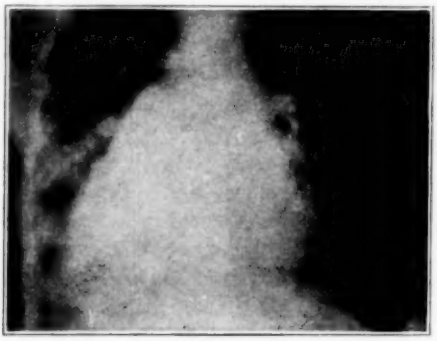


Fig. 6.—Note the large globular erect heart without any evidences of flattening of the subcardial diaphragm to the right of the median line.

The inner part of the left costal margin was slightly diminished in its laterad movement, but the outer half moved readily outward in inspiration. During systole and diastole a loud murmur was audible, which had its maximum intensity at the right border of the manubrium. The pulse had a celer character of moderate excursion. Figure 6 was taken at the time, and shows the moderate globular enlargement of the heart.

A few weeks later surgical relief was attempted, but the patient succumbed during the operation.

Although this patient exhibited marked signs of venous and hepatic stasis he was able to walk about, and although he could exercise little he did not suffer from air hunger when at rest. These facts, together with the absence of pulmonary edema and the absence of ectasis of the right auricle, justified the diagnosis of arteriovenous fistula. The location and contour of the right heart border and the inferior contour of the heart as revealed by the movements of the costal borders, are

the essentials in making a diagnosis in such cases as this. One may be greatly misled if the presence of cardiac enlargement, pulsus celer and the murmurs are accepted as proof of venous stasis from cardiac incompetence.

CARDIAC ENLARGEMENT

The behavior of the heart in arteriovenous fistula is amazing. The large and vigorous impulse that takes in the entire precordial aspect of both ventricles may lead one to overestimate the size of the heart and erroneously make a diagnosis of cardiectasis. When the A-V opening is closed, the impulse over the area of the right ventricle ceases immediately, and only the apical impulse of the left ventricle is perceptible. This change occurs directly after the closing of the arteriovenous fistula, but in severe cases, like the first one described, the percussion borders will not return to the normal limits until after two weeks. In our second case, which was complicated with arteriosclerosis, this change in the character of the precordial impulse could be produced at will by alternately compressing and releasing the femoral artery above the site of the fistula. When the A-V communication is open, the diastolic-systolic excursion of the heart is increased and the heart assumes a globular contour, although the area of precordial projection may be little changed. The deception is quite like that experienced in estimating the size of the heart in acute exophthalmic goiter. The examiner is likely to overestimate the size of the heart in this disease, because the systolic excursion is increased to accommodate an increased minute volume flow of blood. The impulse becomes accessible over the entire precordial area, and the heart is therefore assumed to be much enlarged. Only accurate percussion of the borders of the heart and study of the costal margin movements save one from this error. In acute exophthalmic goiter the costal margin movements never indicate any flattening of the subcardial diaphragm. In chronic exophthalmic goiter that presents evidences of myocardial decompensation and renal disease, the subcardial diaphragm will be flattened as occurs in cardiectasis from other causes.

In producing these cardiac changes experimentally we had no success in survival experiments because in such experiments we could not obtain any great changes in blood pressure—the A-V leak was insufficient. However, when the proximal ends of the abdominal aorta and cava were united by a U-tube and the thorax and pericardium opened, we had a satisfactory view of the two ventricles and the right auricle, and the changes in the size and excursion of these parts were plainly in view as the A-V communication was alternately closed and opened by compressing and releasing the abdominal aorta. Under the fluoroscope the heart was seen to swell into a globular contour but was little enlarged. Roentgenograms were then taken with the tube 6 feet

(182.8 cm.) away. Figure 7, *A* and *B*, shows the difference in the contour of the heart when the A-V flow was closed and free. Later the thorax was freely opened, artificial respiration begun and the pericardial sac opened and used as a support on which the heart rested. On opening and closing the A-V path, the heart was seen to respond in a manner that suggested the changes in excursion and celerity of the arterial wall from the same cause. The ventricles visibly swelled and greatly increased their excursion as the communication was opened, but the right auricle increased little in size and showed a comparatively slight increase of diastolic-systolic excursion. The increase in volume and excursion of the ventricles was plainly a compensatory effect to meet the need of the increased cardiac output that resulted from the arterial

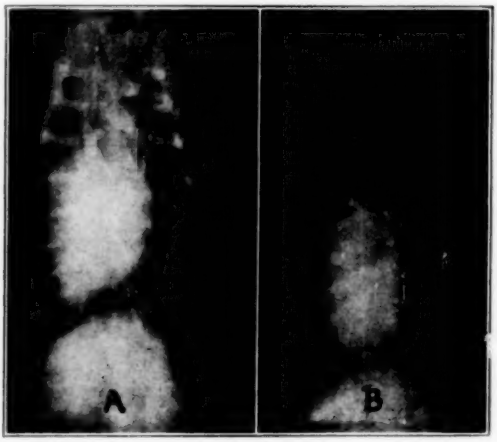


Fig. 7.—The aorta and cava of the dog were connected by a U tube. *A* is a 6 foot roentgenogram with the arteriovenous communication closed. *B* is a 6 foot roentgenogram with the arteriovenous communication opened. Note the change in contour with slight increase in the transverse diameter of the heart.

leak. Ten c.c. of 1 : 1,000 epinephrin were then injected into the jugular vein at intervals of ten minutes. The first few injections caused the heart to increase in size, and the aorta became greatly distended and elongated, so that it resembled the elongated and dilated sclerosed aorta in patients with a high degree of peripheral arterial resistance. After several repetitions of the epinephrin injections, the heart dilated from incompetence and went into fibrillation of auricle and ventricle. As decompensation occurred, attended by great ectasis of the right ventricle and auricle, one perceived the striking contrast between ectasis of the heart chambers and compensatory dilatation in response to an

increase of minute volume flow. Why the subcardial diaphragm is flattened in ectasis and not in compensatory dilatation was apparent. In cardiectasis there was great enlargement and downward extension of the right auricle and base of the right ventricle, whereas in compensatory dilatation there was an increase in the circumference of the mesocardium but no depression of the ventricular base or of the auricle as the circumference of the ventricle enlarged.

Cardiac enlargement compensatory for an increased volume flow produces a globular enlargement restricted to the mesocardium. There is slight if any dislocation of the apex, and the circumference at the base of the heart and at the atrioventricular sulcus is not increased. The heart remains in an erect position and does not encroach on the diaphragm. In arteriovenous fistula, chlorosis and acute exophthalmic goiter, the heart takes on this globular contour and increase of its middle circumference in response to the enlarged minute volume flow of blood. The diastolic-systolic excursion of the ventricles is enlarged. The force and area of precordial excursion of the ventricles are greatly increased and give the impression of great cardiac dilatation, when in reality percussion, movement of the costal borders, and the roentgen ray all indicate only a moderate globular enlargement of the ventricles. In acute exophthalmic goiter, a degree of volume increase that would suffice in myocardial disease to depress the subcardial diaphragm will not show any modification of inspiratory movements of either costal border. The reason for this is quite apparent if the changes are observed in heart volume and contour when epinephrin in large amounts is given to a dog with a large A-V fistula. When the fistula is open, the heart increases in its midcircumference and diastolic-systolic excursion without encroaching downward, but as acute dilatation and fibrillation follow the large dosage of epinephrin, the circumference of the ventricles at the atrioventricular sulcus greatly enlarges, the right auricle protrudes with a large semilunar contour to the right of the base of the ventricle, and the heart encroaches on the diaphragm. These observations provided us with a satisfactory explanation for the discrepancy between the costal border movements in exophthalmic goiter and in cardiac disease, when apparently both conditions should produce corresponding effects on the costal border movements.

From our clinical observations and animal experiments we were convinced of the ventricular enlargement that immediately attends short-circuiting of the circulation through an A-V opening. When the teleoroentgenograms were made, however, they were disappointing. They did not show as much enlargement in the transverse direction as we expected to see. The cardiac enlargement as perceived by clinical examination and by direct inspection in animal experiments indicated

the primary enlargement to be chiefly in an anteroposterior diameter in the early stages of the disease, and enlargement of the transverse diameter to be a later development.

To present graphic evidence of ventricular enlargement as a promptly developing sign of A-V fistula, the size of the heart was recorded by a plethysmograph. The abdominal aorta and cava were united by a U-tube, the thorax opened and artificial respiration employed. The ventricles only were included in the plethysmograph. The upper tracing in Figure 8 shows the blood pressure taken by a mercury manometer from the carotid artery. The lower tracing is that of the plethysmograph. *C* marks the closure and *O* the opening of the A-V communication. The excursions of the plethysmograph were graduated immediately after the experiment by introducing measured quantities of water

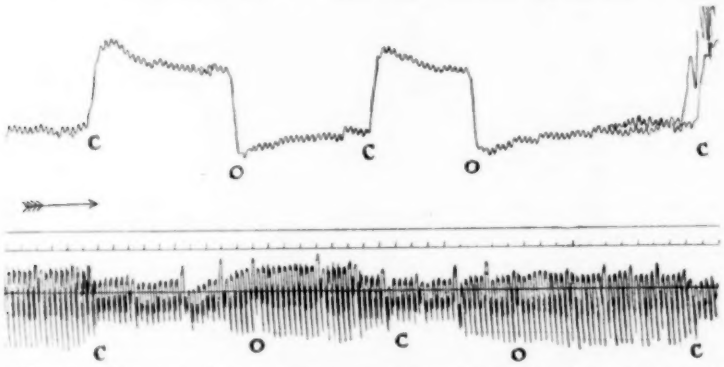


Fig. 8.—The upper line is a mercury manometer tracing from the carotid artery. The lower line is from the plethysmogram of the heart. The time recorded is in seconds. At *C* the arteriovenous communication was closed, and at *O* it was opened.

into the system. When the results of the graduation were applied to the tracings, it was found that the excursion of this heart amounted to 6 c.c. when the A-V opening was closed, and 11 c.c. when opened. This measurement is in all probability exaggerated by the swing of the registering lever, but it is not surprising after the change in excursion has been observed in an animal experiment. The time marker is in seconds.

Figure 9 is a tracing taken on a fast drum to show the working of the plethysmograph. The up stroke traces diastole and the down stroke systole.

These observations show how a heart may be enlarged anteroposteriorly and fail to show by percussion or roentgen ray any transverse enlargement. This is true of well compensated cases of mitral

stenosis when only the right ventricle is enlarged, and it is also true in exophthalmic goiter when both ventricles are enlarged and the auricles are not. The only physical sign that betrays the enlargement is the enlargement of the area of precordial impulse due to the right ventricle partaking of this activity as well as the apex of the left ventricle. When a clinician establishes the evidences for anteroposterior cardiac enlargement, he should not recede from his position because the roentgen ray fails to reveal an enlargement of the precordial area.

THE HEPATIC PULSE

The physical sign of striking importance that remains for discussion is the hepatic pulse. It will be remembered that in three of the reported cases—the two in which the A-V fistula formed in the femoral vessels after gunshot wounds, and the one in which the fistula formed between the carotid and jugular after a sharp blow from the long wooden

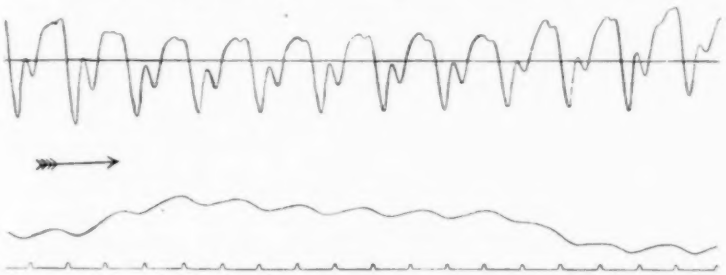


Fig. 9.—This plethysmographic tracing is from the same experiment in which the tracing in Figure 8 was made, and merely shows the correct working of the plethysmograph. The time recorded is in one-fifth seconds.

handle of a mop—there were systolic pulsations in the liver. In the case of the woman with the gunshot wound, as the artery above the fistula was compressed the hepatic pulse disappeared with the cardiac systole that followed the arterial compression, so that there can be no doubt that the systole of the right ventricle played no part in producing the hepatic pulse. It depended on two factors—an adequate distention of the cava, and a direct pulse wave from the artery into the tributaries of the cava. In our experimental animals there was no hepatic pulse palpable or visible when the abdomen was opened and the liver brought plainly into view, and in none of them were we able to procure sufficient pressure in the cava to obtain an hepatic pulse. It might have been expected that when the lumen of the aorta was connected with the cava there would be a considerable rise in the cava pressure, but that was not the case. Our experiment was of such short duration that the increased output of the heart was adequate to care for this contingency.

In the clinical cases the problem of hydraulics of blood flow must have been nearly, although not quite, identical with that in our experimental animal, the essential factor being the cardiac inability to compensate over a prolonged period for the enlarged minute volume flow necessitated by the arteriovenous communication.

The hepatic pulsation in our patients was not an index or measure of cardiac decompensation. It came directly from the arteriovenous opening, but should the arteriovenous leak be ever so large that alone will not suffice to produce an hepatic pulse. The pulsation of the liver is not obtained until the factor of large elevation in venous pressure is added. The arteriovenous leak does not suffice to produce the liver pulse until the cava pressure increases as a result of the incompetence of the heart to supply the increased output demanded as a result of the arteriovenous fistula. Under such conditions, closure of an arteriovenous communication produces an amazing cure. By this procedure the venous system as well as the myocardium profits directly. The work of the heart is greatly lessened, and both the direct and the indirect source for venous stasis is corrected. Our patient who was operated on and promptly restored to health after so long and exhausting an illness submitted to an examination two years after the operation. He was then in perfect health and seemingly was concerned only about his pension, which had been granted on the basis of total disability.

VENTRICULAR ECTOPIC TACHYCARDIA COMPLICATING DIGITALIS THERAPY *

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Paroxysmal tachycardia originating from an ectopic focus in the ventricle is a relatively rare type of cardiac arrhythmia. Robinson and Herman,[1] in 1921, found reports of only sixteen cases, not all of which they accepted as proved, and to which they added four additional cases.

This type of paroxysmal tachycardia can be differentiated from that of auricular origin only by the help of the electrocardiograph. Even then, unless the electrocardiogram contains the beginning or the ending of the paroxysm, it is not always possible to determine the exact origin of the rhythm, since it is known that in some instances of paroxysmal auricular tachycardia the ventricular complexes may be aberrant, due to imperfect conduction in the ventricular conduction paths during the rapid rate.[2]

When the tracing does not contain the first beat of the paroxysm, search should be made for evidence of the P wave, and if it can be shown that the auricles are beating at a different rate from that of the ventricles, the paroxysm is almost surely ventricular in origin. Electrocardiograms taken shortly before or after the paroxysm of tachycardia should be examined; if they contain isolated ventricular extrasystoles which are an exact replica of the complex which is regularly repeated during the paroxysm, it is the more probable that the latter is of ectopic ventricular origin.

Lewis [3] pointed out the relation of ventricular ectopic tachycardia to thrombosis in the coronary artery. Robinson and Hermann,[1] in the paper already mentioned, also emphasized the frequent association of this arrhythmia with coronary occlusion and infarction of the myocardium.

Later Lewis and Levy [4] observed ventricular ectopic tachycardia in cats under the influence of chloroform and epinephrin.

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* From the Heart Laboratory of the Boston City Hospital.

1. Robinson and Hermann: Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, Heart **8**:59 (Feb.) 1921.

2. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920, p. 262.

3. Lewis, T.: The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, Heart **1**:98, 1909-1910.

4. Lewis and Levy: Heart Irregularities, Resulting from the Inhalation of Low Percentages of Chloroform Vapour and their Relation to Ventricular Fibrillation, Heart **3**:99, 1911-1912.

In his study of the action of strophanthin on the cat's heart, S. A. Levine [5] noted this same arrhythmia. In one experiment it did not appear until 90 per cent. of the minimum lethal dose had been injected, and without the previous appearance of extrasystoles.

The administration of quinidin sulphate has been followed by the appearance of ventricular ectopic tachycardia, and dogs have occasionally died with this arrhythmia.[6] R. L. Levy [7] reports three cases in man. Fortunately they were of short duration, lasting always less than twenty hours, and sometimes disappearing in the course of three hours after the last dose of quinidin was given. Another case was reported by W. J. Kerr and W. L. Bender; [8] certainly some of the curves appear to be examples of ventricular ectopic tachycardia.

Eggleston and Wyckoff [9] noted runs of this form of ventricular tachycardia in one case in their study of the absorption of digitalis in man; a good recovery followed. C. Schwensen,[10] of Copenhagen, has reported a fatal case of ventricular ectopic tachycardia as a complication of the administration of digitalis. The electrocardiograms of the other case, described in Schwensen's paper, showed ventricular extrasystoles of multiple origin but not a true paroxysm of tachycardia of ventricular origin.

Wolferth and McMillan [11] have recently reported four more cases of ventricular ectopic tachycardia. They are disinclined to credit the action of digitalis as a cause; in their cases digitalis was used in only one of the four, and the weight of evidence was against the paroxysm of tachycardia being drug induced. These same observers point out that the combination of auricular flutter or fibrillation with paroxysmal tachycardia is extremely rare (except when the latter is caused by drugs), until their report only one case of each having been recorded, both by Gallavardin.[12]

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5. Levine, S. A.: The Action of Strophanthin on the living Cat's Heart, J. Exper. Med. **29**:485 (May 1) 1919.

6. Cohn, A. E., and Levy, R. L.: Experimental Studies of the Pharmacology of Quinidine, Proc. Soc. Exper. Biol. & Med. **18**:283, 1921.

7. Levy, R. L.: Clinical Studies of Quinidine, Arch. Int. Med. **30**:451 (Oct.) 1922.

8. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart-Block while Under Quinidine Sulphate Therapy, Heart **9**:269 (Dec.) 1922.

9. Eggleston and Wyckoff: The Absorption of Digitalis in Man, Arch. Int. Med. **30**:133 (Aug.) 1922.

10. Schwensen, C.: Ventricular Tachycardia as the Result of the Administration of Digitalis, Heart **9**:199 (April) 1922.

11. Wolferth and McMillan: Paroxysmal Ventricular Tachycardia. Report of One Case with Normal Type of Auricular Mechanism and Three with Auricular Fibrillation, Arch. Int. Med. **31**:184 (Feb. 15) 1923.

12. Gallavardin: Tachycardia Paroxystique Ventriculaire, Arch. d. mal. du coeur **13**:121 (March) 1920. Tachycardia Ventriculaire Terminale, Arch. d. mal. du coeur **13**:207 (May) 1920.

CASE REPORTS

CASE 1.—*History.*—A housewife, aged 50, entered the Boston City Hospital, Sept. 24, 1922. She complained of dyspnea, precordial pain, palpitation, a slight cough, swelling of the ankles and general weakness. One year ago she first noted dyspnea on slight exertion; this was accompanied by a mild nonproductive cough. The symptoms had gradually increased and during the two months before she entered the hospital there had been palpitation, precordial pain and edema of the ankles. Measles was the only disease recalled. She said she had not had rheumatic fever, chorea, tonsillitis, pneumonia, typhoid fever, puerperal sepsis, any acute fever or venereal disease. She weighed 200 pounds (90.7 kg.); her weight had been unchanged for years.

Physical Examination.—The patient was markedly cyanotic and orthopneic, and her expression was distressed. Visible throbbing of the carotid arteries was noted. The lungs were normal to percussion and auscultation except for a

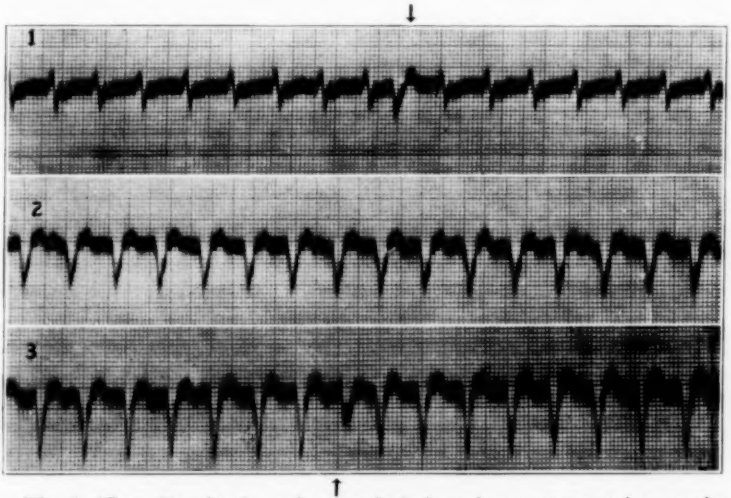

Fig. 1 (Case 1).—At the points marked there is an apparent interruption of the paroxysm. Careful scrutiny of the tracing discloses an irregular activity of the auricles. In this and the subsequent electrocardiograms the course abscissas mark off periods of 0.2 of a second; the finer ordinates have a value of 0.1 millivolt.

few râles at the bases. The heart impulse was palpable in the fifth interspace outside the midclavicular line; by percussion the cardiac borders were found to be 4 cm. to the right and 14 cm. to the left of the midsternal line. There was a systolic murmur at the apex, well transmitted to the base and to the left axilla. A soft diastolic murmur was noted at the aortic area and well transmitted along the left sternal margin. The rhythm was absolutely irregular, the apex rate was from 130 to 140, the radial, 98 to 110. The abdomen was distended. There were shifting dulness and fluid wave. The liver was not felt. There was considerable soft edema of the lower legs. The blood pressure was: systolic 160 to 170, diastolic 110 to 120. The Wassermann reaction was negative.

Course of Illness.—September 27: The patient was much relieved; the edema was almost gone. The heart rate was about 90, the rhythm irregular,

the pulse deficit almost gone. The rhythm was apparently that of auricular fibrillation with some ventricular extrasystoles. The patient was nauseated early in the morning.

September, 29: The patient was very restless sleeping only in naps, and trying to get out of bed frequently during the night. She vomited in the morning, had a cold perspiration and talked at random. The heart action was observed to become rapid suddenly and regular. This was displaced after about two minutes by the former irregular rhythm at the rate of about 90 per minute. These two rhythms alternated at intervals of one to three minutes for about three quarters of an hour and then the regular tachycardia of a rate of about 150 per minute became permanent. An electrocardiogram confirmed the clinical diagnosis of ventricular ectopic tachycardia.

September 31: The ventricular tachycardia had persisted and the patient had lost ground gradually with signs of progressive heart failure of the congestive type. Death occurred two days and three hours after the onset of the tachycardia.

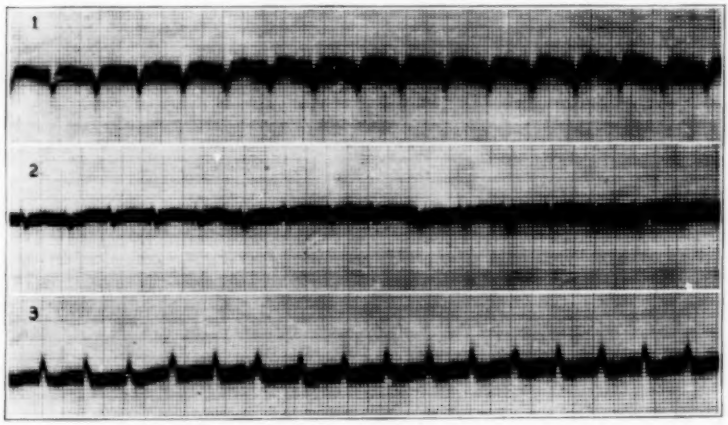

Fig. 2 (Case 2).—Ventricular ectopic tachycardia, rate 140.

Case 2.—A man, aged 63, entered the Boston City Hospital on Dec. 23, 1922. He complained of periodic shortness of breath. During the past two years he had had attacks of shortness of breath lasting about one hour each. Twenty-four hours before entering the hospital a similar attack began. He was raising gas from the stomach, freely. There was also a dry cough and moderate precordial pain with the present attack. He had had excellent health until the present illness.

Physical Examination.—This revealed: considerable cyanosis, respiration rapid, labored and accompanied by audible tracheal râles. The lungs showed dulness at the bases with moist râles throughout. There was percussion dulness of the heart measuring 4.5—16.5 cm. The rhythm was absolutely irregular, the rate rapid and a large pulse deficit was noted. There was marked tenderness of the liver. Soft edema was present from the feet to the thighs and over the lower part of the back.

Course of Illness.—December 24: The heart sounds were almost regular, interrupted by occasional extrasystoles. The patient appeared to be much relieved.

December 28: In the forenoon a regular tachycardia, rate 140, appeared suddenly. This persisted until late in the afternoon, when there were periods during which the heart rate was 58 per minute and regular except for occasional coupling. During the tachycardia there was moderate dyspnea and precordial pain. Death occurred suddenly during the night.

Necropsy.—The pericardium contained 30 c.c. of clear fluid. The heart weighed 320 gm. On the surface were numerous small "milk patches." The coronary arteries showed on the surface as opaque, white wavy lines. The myocardium was reddish brown; the consistency was firm. The right auricle was somewhat dilated. The cusps of the aortic valve were thickened and yellow in places, and one old fibrous vegetation persisted. The mitral valve was somewhat thickened. The measurements were: tricusped valve, 14 cm.; pulmonary valve, 8.3 cm.; mitral value, 10.5 cm.; aortic valve, 7.3 cm.; the left ventricle was 1.3—2 cm., the right ventricle 0.5 cm. The coronary arteries showed patches of sclerosis. There was a moderate amount of sclerosis, in the aorta, most marked in the lumbar region.

Anatomic Diagnosis.—The diagnosis was hypertrophy and dilatation of the heart; moderate arteriosclerosis of the aorta and coronaries.

Case 3.—A woman, aged 80 years, entered the Boston City Hospital on Feb. 5, 1923. During the preceding months the patient had been dyspneic

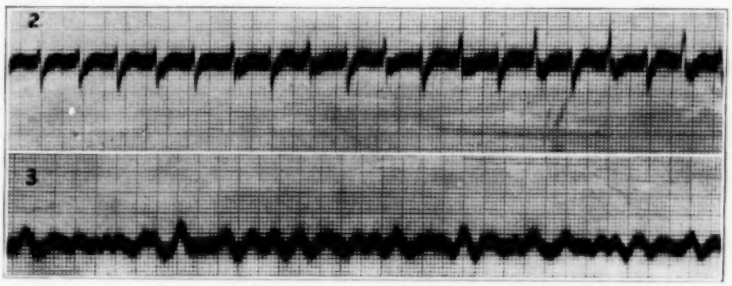

Fig. 3 (Case 3).—Lead II, ventricular ectopic tachycardia, rate 170. Note transition to an alternating mechanism in the latter half of the tracing. Lead III ventricular fibrillation. About 25 to 30 seconds time elapsed between the two tracings.

on slight exertion. There had been frequent attacks of palpitation during the two preceding months. She had done much manual labor until six weeks before, when her ankles became swollen and the dyspnea and palpitation increased. She had been confined to bed for four weeks before entering the hospital and had grown worse. The swelling now extended to the legs and the abdominal wall. She had had measles, mumps and whooping cough when a child and one or two attacks of tonsillitis each winter during childhood. There was no history of rheumatic fever, chorea, scarlet fever, etc. Her maximum weight before the onset of the swelling was 135 pounds (62.2 kg.).

Physical Examination.—The patient was well developed and well nourished. She had marked dyspnea and considerable cyanosis. The cervical veins were engorged and pulsating markedly. The bases of both lungs were dull; there was flatness and diminished tactile fremitus at the right base below the mid-scapular region and extending to the right lower front. There was bronchial breathing and egophony above this area, with a few scattered râles. There were many moist bubbling râles in the left side of the chest. The heart impulse was palpable in the fifth space at the anterior axillary line, accompanied by a

systolic thrill. There was absolute arrhythmia. The apex rate was 124, the wrist rate 78; the deficit 46. There was a loud first sound at the apex with systolic and mid-diastolic murmurs. The pulmonic second sound was louder than the aortic second sound, but not accentuated. The abdomen was slightly distended, the wall edematous; no shifting dulness was detected. The edge of the liver was 2 cm. below the costal margin in the right mamillary line.

Thick, brawny edema was present in the legs and dependent parts of the trunk. The blood Wassermann reaction was negative.

Course of Illness.—February 6: The heart action suddenly changed to a regular tachycardia—rate 160.

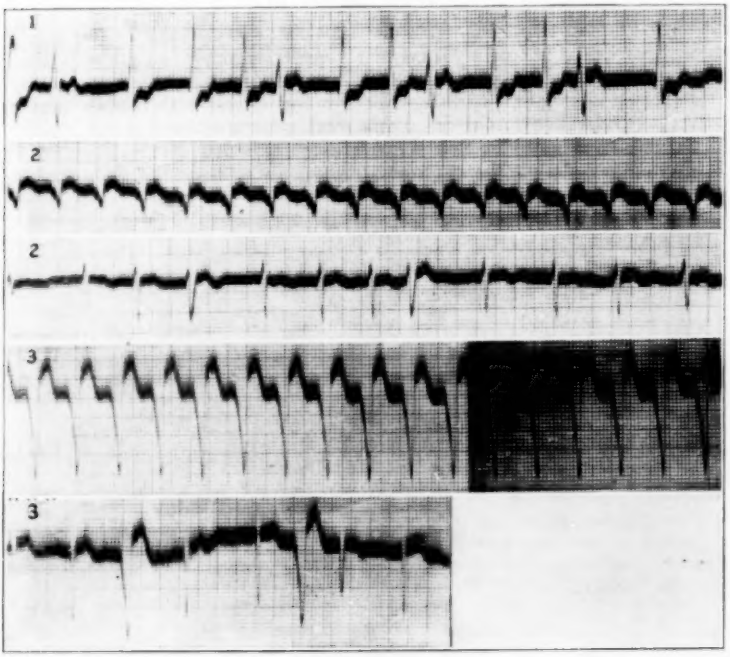

Fig. 4 (Case 4).—Ventricular ectopic tachycardia in tracings 2 and 4 (counting from above downward); auricular fibrillation with ventricular extrasystoles replicas of the ventricular complexes in the tracing just above. An intervals of but a few seconds elapsed between the individual tracings.

February 7: The regular tachycardia continued but was interrupted by periods of a few seconds during which the heart rate was much slower, estimated at about 50 to 60 per minute.

An electrocardiogram was taken. The first photograph showed ventricular ectopic tachycardia, and the remaining three ventricular fibrillation. The patient was resting comfortably just before the tracing was made; death occurred peacefully as the ventricular fibrillation was recorded. Examination of the anterior chest just previous to the taking of the electrocardiogram disclosed no râles, and no tracheal râles were audible as death ensued.

CASE 4.—A man, aged 47, entered the hospital on July 7, 1921, complaining of dyspnea and palpitation. For ten months he had had a sense of constriction under the sternum after exertion. This had gradually become more marked until walking on the level caused severe precordial pain. One month before swelling of the ankles and lower legs became manifest. The patient had been dyspneic, weak and afflicted by a cough with free expectoration during the week before entering the hospital. He had not had children's diseases. His cardiorespiratory history was negative. One year before he had had an operation in this hospital for the removal of calculi from the left kidney. His wife died of heart disease. He had four children living and well and one stillborn child.

Physical Examination.—The patient was orthopneic. Many coarse râles were heard in the lungs. The heart impulse was in the fifth space, 2 cm. outside the nipple line. The left border of deep cardiac dulness was 16 cm.

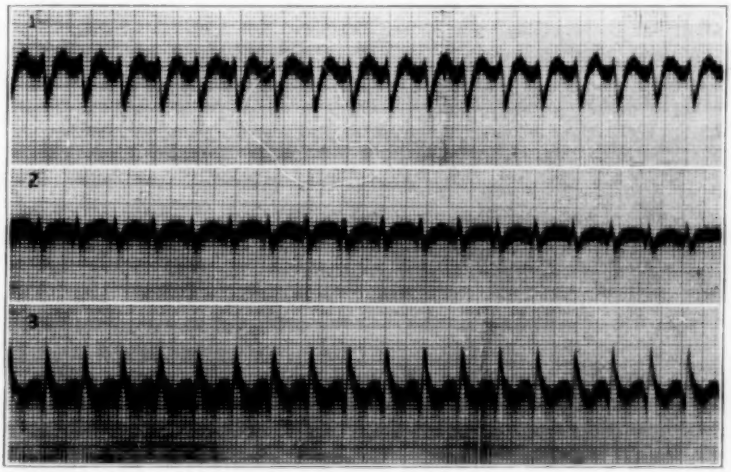

Fig. 5 (Case 5).—Ventricular ectopic tachycardia, rate 174.

from the midsternal line; the right border was not obtained. The rhythm was absolutely irregular; no murmurs were heard. The abdomen was distended. The liver was palpable 5 cm. below the costal margin in the right axillary line; it was slightly tender. There was marked edema from the ankles to the knees. The blood Wassermann reaction was negative.

Course of Illness.—July 11: The patient had improved a little. His heart rate varied from 98 to 110. In the morning there were runs of a regular tachycardia, rate 146, lasting from one half to one and one half minutes. An electrocardiogram (Fig. 4) showed ventricular ectopic tachycardia alternating with periods of auricular fibrillation and ventricular premature beats.

July 12: The runs of the regular tachycardia had ceased.

Subsequent History.—There was no further appearance of the ventricular ectopic tachycardia. The mechanism of auricular fibrillation continued, and the patient's condition remained stationary. Death from progressive failure of the heart occurred on Sept. 12, 1921.

CASE 5.—A woman, aged 60, admitted to the hospital on Jan. 7, 1923, had known of her heart disease since 1902; but she was not confined to bed because of it.

Physical Examination.—She was moderately dyspneic, not cyanosed. The heart impulse was palpable in the fifth space, just outside the midclavicular line; percussion corresponded. There was a systolic murmur with a first sound at the apex, transmitted to the base and axilla. The supracardiac dulness at the first space measured 2 by 1 cm.

Course of Illness.—January 12: The patient had been slightly better. At noon the heart action changed to a fixed, regular tachycardia, rate 174 per minute. The tachycardia persisted into the night, during which it disappeared. An electrocardiogram (Fig. 5) showed ventricular ectopic tachycardia.

January 13: The regular tachycardia returned for a few hours during the afternoon.

January 14: During the evening the third and last attack of regular tachycardia appeared and ceased during the night.

January 15: An electrocardiogram (Fig. 6) showed normal rhythm with multiple ventricular extrasystoles. The patient died from progressive heart failure on January 20.

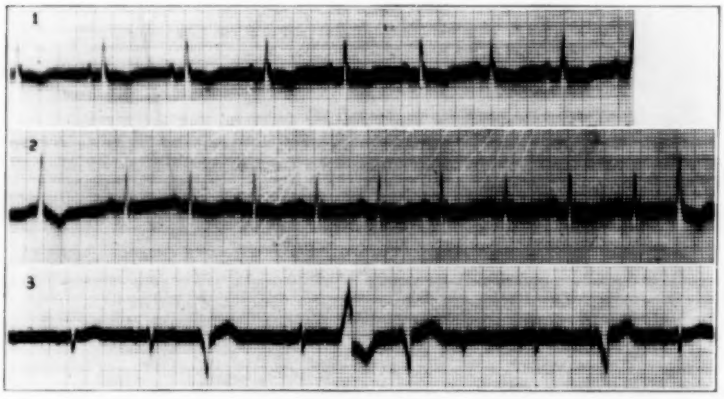

Fig. 6 (Case 6).—Normal rhythm interrupted by ventricular extrasystoles.

DIGITALIS RECORDS

The recent report of Eggleston and Wyckoff [9] has shown that the approximate total amount of digitalis, when using preparations of standard potency, may be calculated on the basis of one cat unit to 10 pounds (4.5 kg.) of body weight of the patient. The tincture of digitalis was employed in the treatment of the above five patients, and in a tincture which has not deteriorated there is one cat unit per cubic centimeter. According to Hatcher and Eggleston.[13] The amount of digitalis indicated, then, may be calculated by the simple procedure of inserting a single decimal point in the figure representing the patient's weight in pounds; for example, if the patient weighs 153 pounds (69.3 kg.), the

13. Hatcher and Eggleston: Observations on the Keeping Properties of Digitalis and Some of Its Preparations, Am. J. Pharm. **85**:203, 1913.

approximate amount of the drug is 15.3 c.c. H. E. B. Pardee has recorded that the average daily excretion or using up of digitalis when using a tincture of standard potency, is 1.5 c.c. Therefore, when the administration of the digitalis is continued, as is usual, over a period of days, an allowance of 1.5 c.c. per day should be made for what is used up; the amount remaining, after subtracting 1.5 c.c. for each day of the administration from the total amount given, indicates the amount of the tincture of digitalis which may be estimated to be active in the patient at any given time.

In another report [14] evidence has been presented which supports the belief that the tincture administered to the foregoing patients was of standard potency. It is fully appreciated that there exists some degree of error in arbitrarily using Pardee's average of 1.5 c.c. in case the individual patient used up the drug faster or slower (Pardee found 10 and 40 minims [0.6 c.c. and 2.5 c.c.] the extremes). Nevertheless, the method offers a means of estimating the amount of digitalis that was active in the patients at the time of the appearance of the paroxysms of ventricular tachycardia, and it seems worth while to compare this with the amount indicated for full therapeutic digitalization according to the Eggleston method of calculation.

The digitalis records of the five patients are given below; they may, perhaps, be more easily visualized by a glance at the table.

Case 1.—Body weight, 200 pounds; given 8 c.c. of tincture of digitalis and then divided doses for 4.6 days; total amount of digitalis, 50 c.c. Subtracting 6.9 c.c. leaves 43.1 c.c., which is 215 per cent. of the 20 c.c. indicated.

Case 2.—Body weight 160 pounds; given 16 c.c. of tincture of digitalis and then 2 c.c. from four to six times a day for 5.3 days; total amount of digitalis 88 c.c. Subtracting 8 c.c. leaves 80 c.c., which is 500 per cent. of the 16 c.c. indicated.

Case 3.—Body weight 135 pounds (before the onset of edema); given 4 c.c. of tincture of digitalis and then 2 c.c. in repeated doses for two days; total amount of digitalis 23 c.c. Subtracting 3 c.c. leaves 20 c.c., which is 148 per cent. of the 13.5 c.c. indicated. (The ventricular tachycardia appeared after only 11 c.c. of digitalis had been given, but there was great probability that the drug had already been administered by the patient's physician before admission to the hospital.)

Case 4.—Body weight 190 pounds; given 12 c.c. of tincture of digitalis and then divided doses until the fifth day; total amount of digitalis, 49 c.c. Subtracting 6 c.c. leaves 43 c.c., which is 226 per cent. of the 19 c.c. indicated.

Case 5.—Body weight 155 pounds; given 8 c.c. of tincture of digitalis and then divided doses for five days; total amount of digitalis, 35.3 c.c. Subtracting 7.5 c.c. leaves 27.8 c.c., which is 179 per cent. of the 15.5 c.c. indicated.

As can be seen by these summaries of the digitalis records, or in Table 1, the amounts are well in excess of that estimated for therapeutic digitalization by the Eggleston method. The figure of 148 per cent. in

14. Reid, W. D.: Some Toxic Effects of Digitalis, J. A. M. A. **81**:435 (Aug. 11) 1923.

Case 3 probably does not represent the total amount of the drug which the patient had received.

The patient in Case 3 died from a change of the mechanism to that of ventricular fibrillation, as shown in the electrocardiograms (Fig. 3). The sudden death of the patient in Case 2 during the night was quite possibly of similar nature. This change has been observed by Lewis[15] and others in experimental work on animals; so far as the writer is aware, this is the first record of the event in a human being (that is, the sequence paroxysmal tachycardia of ventricular origin, ventricular fibrillation and death). It is worthy of mention that in both Cases 2 and 3 the clinicians in charge of the treatment continued the administration of the drug after the onset of the regular tachycardia. In Case 1 the drug was temporarily omitted, but after twelve hours a single dose of a digitalis preparation was injected subcutaneously; the regular tachy-

TABLE 1.—*Digitalis Records in Cases Reported*

Case	Body Weight in Pounds	Total Digitalis in C.c.*	Relation to Amount Calculated by Eggleston Method†	Number of Days to Course of Digitalis	Digitalis Omitted	Rhythm	Death
1	200	43.1	215%	4.6	No	Persisted	2¼ days
2	160	80	500%	5.3	No	Persisted	15 hours
3	135	20**	148%**	2**	No	Persisted	24 hours
4	190	43	226%	4	Yes	Ceased	2 months
5	155	27.8	179%	5	Yes	Ceased	8 days

* After subtracting 1.5 c.c. per day for the number of days the drug was administered.
** Probably had received digitalis, amount unknown, before admission to the hospital.
† In the discussion of my paper (footnote 14) Dr. Eggleston said I should have used the figure 1.5 cat units per 10 pounds (4.5 kg.) of body weight as I was dealing with the galenical tincture, whereas he employed a purified tincture. Correcting these figures according to Eggleston's suggestion, the percentage relation is found to be 143, 333, 100, 150 and 119 per cent. in the five cases, respectively. In my opinion, an overdosage is yet in evidence.

cardia persisted until the death of the patient. In Cases 4 and 5 the prompt discontinuance of the digitalis was followed by recovery from the ventricular ectopic tachycardia, although death resulted later from heart failure.

CONFUSION WITH FLUTTER OF THE AURICLES

In each case the onset of the tachycardia of regular rhythm and fixed rate caused a presumptive diagnosis of auricular flutter to be made; experience with the first case and familiarity with the reports of experimental work enabled me to make the correct diagnosis in the remaining four instances. Of course, resort to graphic methods of examination, preferably an electrocardiogram, was necessary to prove the diagnosis.

In view of what is known of cardiac physiology, it appears unwarranted to believe that the action of digitalis causes the mechanism of

15. Lewis: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920, p. 330.

auricular fibrillation to change to that of flutter. It is well known that the reverse process, that is, flutter to fibrillation, occurs in a considerable percentage of cases of auricular flutter treated with digitalis; such is an established therapeutic measure. Quinidin sulphate, it is true, often changes auricular fibrillation to flutter, and perhaps this accounts for some of the confusion of thought on the subject. Lewis and his co-workers have clearly demonstrated that the wave is circulating faster in auricular fibrillation than in flutter, averaging 450 in the former and 300 in the latter. T. S. Hart [16] has pointed out that when digitalis is given the auricular waves usually become smaller and more rapid; I have confirmed the acceleration. This fact is in accordance with the extensive data on the mechanism of auricular flutter and fibrillation reported by Lewis and his co-workers in a series of papers [17] published in 1920 and 1921. Lewis [18] has reaffirmed the increase of the auricular rate, that is, the acceleration of the circus movement in flutter and fibrillation of the auricles, by the action of digitalis.

It is because of the clinical resemblance to auricular flutter that it is important that ventricular ectopic tachycardia should be accurately diagnosed. For if the regular tachycardia be thought to be due to flutter of the auricles, the indication would be to give more digitalis with the hope of restoring, as not infrequently happens, the normal rhythm or at least of causing sufficient delay in the auriculoventricular conduction to block some of the auricular impulses and to permit the ventricle to beat at a slower rate. But, if the condition happens to be a tachycardia rising in the ventricle, no amount of A-V heart block will avail, and the further administration of digitalis may prove fatal.

TREATMENT

I am unaware of any successful treatment of ventricular ectopic tachycardia, and this makes the seriousness of the onset of this arrhythmia all the more evident. Vagal stimulation and the injection of atropin in both small and large doses was tried without benefit. Quinidin sulphate might be tried, but it too has caused this rhythm to appear.

The obvious thing to do is to remove the cause, that is, omit the digitalis. Ventricular ectopic tachycardia, in the present state of our knowledge, is better to avoid than to treat.

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16. Hart, T. S.: Quinidine in Auricular Fibrillation, with Some Observations on Its Use in Combination with Digitalis, Arch. Int. Med. **30**:593 (Nov.) 1922.

17. Lewis et al.: Heart **7**:127, 191, 247 and 293, 1920; **8**:37, 83, 141, 171 and 193, 1921.

18. Lewis: The Action of Digitalis in Case of Auricular Fibrillation and Flutter, Am. J. M. Sc. **164**:157 (Aug.) 1922.

SUMMARY AND CONCLUSIONS

Ventricular ectopic tachycardia is a relatively rare arrhythmia.

It cannot be differentiated from auricular ectopic tachycardia without an electrocardiogram and not always even then.

Previous reports of its occurrence, especially those in which it followed the administration of a drug—chloroform, quinidin sulphate, strophanthin and digitalis—have been mentioned.

So far as I am aware, ventricular ectopic tachycardia as a complication of digitalis therapy in man has been previously reported only twice.

The histories of five cases in which ventricular ectopic tachycardia appeared during the treatment of auricular fibrillation by digitalis are recorded.

In one case the change to ventricular fibrillation was recorded electrocardiographically. This is believed to be the first report in which the electrocardiograms show, in man, the sequence ventricular ectopic tachycardia to ventricular fibrillation.

The amount of digitalis administered before the onset of this arrhythmia was well in excess of that indicated by the Eggleston method of calculation.

The condition was confused with auricular flutter and more digitalis given to some of the patients.

A COMPARISON OF CERTAIN METHODS OF TREATMENT AND DIAGNOSIS OF HOOKWORM INFECTION *

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The observations presented in this paper were made from Aug. 16 to Dec. 31, 1922, at the State Hospital for the Insane at Sandy Gallop, Queensland. They are supplementary to the results of an investigation carried out from May 15 to Oct. 31, 1922, at the Hospital for the Insane at Goodna, Queensland.[1] In the investigation at Goodna it had been found that patients were being infected with hookworms of the species *Ancylostoma duodenale* and that the infection rates were highest in the wards containing the less teachable insane. The institution was shown to be outside the belt in which there was sufficient rainfall to permit indigenous hookworm infection of the white population not in institutions or mines, but experiments demonstrated that hookworm larvae could develop in the soil in much diminished numbers even under the local winter conditions of moderate rainfall and cool weather. The investigation showed also that carbon tetrachlorid was much less efficient in the removal of *Ancylostoma duodenale* than would have been expected in view of the successes of other investigators using the drug in the treatment of *Necator americanus* infection.

As all the patients at the hospital at Sandy Gallop had been transferred from the hospital at Goodna, it was to be expected that some of them would have an *Ancylostoma duodenale* infection that they had brought with them. On the invitation of Dr. A. Morrison, medical superintendent, and with his cooperation, and with the approval of Dr. H. Byam Ellerton, inspector of asylums for Queensland, all the patients in the hospital were examined and the infected ones treated until cured by members of the staff of the Australian Hookworm Campaign. The treatments were so arranged that the efficiency of each method used could be measured by the percentage of worms expelled and by the number of cures.

* The work on which this paper is based was conducted with the support and under the auspices of the Department of Health of the Commonwealth of Australia, the International Health Board of the Rockefeller Foundation, and the State of Queensland.

1. Sawyer, W. A.; Sweet, W. C., and Shaw, A. E.: Institutional Hookworm Disease in a Non-Endemic Area, *to be published.*

Sandy Gallop is in the outskirts of Ipswich in southeastern Queensland and lies well inland from the hookworm belt, which is largely limited to the regions of high rainfall along the coast. According to the Commonwealth Meteorologist, the annual rainfall is 34.52 inches, and the greatest amount of precipitation occurs in the summer. The mean temperature for a representative year was 52.9 F. for July, 82.3 F. for January, and 68.5 F. for the year.

The wards of the Hospital for the Insane are supplied with water-flushed closets, and efforts are made to keep the yards as free from soil pollution as possible.

THE PREVALENCE, SEVERITY, AND ORIGIN OF THE INFECTION

Examination of the feces of the 447 patients by the Willis salt flotation method showed that 121, or 27.1 per cent., were infected with hookworms. Seventy-two, or 16.1 per cent., were infected with whipworms (*Trichuris trichiura*), and twelve, or 2.7 per cent., with threadworms (*Oxyuris vermicularis*). No evidence of other intestinal worms was found. As usual, the infection rate for *Oxyuris vermicularis*, as revealed by microscope, was far below the true rate, probably because the ova are deposited low in the large intestine where the contents are no longer liquid. As a result the ova are not mixed throughout the feces and are absent from the majority of fecal specimens taken for microscopic examination. Among 119 patients whose feces were examined after treatment, adult worms of this species were found in eighty-five, or 71.4 per cent.

The 115 female patients in the hospital had a hookworm infection rate of 49.6 per cent., and the 332 males, of 19.3 per cent. The highest rate in any one ward was 63 per cent. in Female Ward 1, and the lowest rate, 8.3 per cent. in Male Ward 1. All the infected patients were adults, and all but eighteen were of the white race.

That at least the greater part of the hookworm infection had been contracted before the patients were transferred from the hospital at Goodna to the one at Sandy Gallop is suggested by the observation that the number of hookworms harbored decreased with the length of stay. Thirty-four patients who had more than ten hookworms had been at Sandy Gallop an average of 5.6 years, and eighty-five who yielded less than ten hookworms had been there an average of 6.9 years, while 326 persons free from hookworms had been in the institution an average of 8.8 years. Among ninety-two patients who yielded hookworms following treatment, fifty-five who had been in the institution from one to five years had an average of 21.6 worms; twenty-seven who had been there from six to ten years had an average of 18.6 worms; and ten who had been there more than ten years had an average of only 8.3 worms. One patient who had been in the institution nineteen years, a period usually considered much longer than

the maximum life of the hookworm, had forty-three hookworms; it would seem probable, therefore, that some infection was being contracted at Sandy Gallop, although it is evident that more hookworms were being lost than gained.

The more frequently the infected patients had gone barefooted, the higher the number of hookworms harbored. The average number of hookworms yielded by fifty-four patients who ordinarily wore shoes was 14.5, while that for thirty-eight who usually went barefoot was 26.2. It is likely that these patients had previously had similar habits when at the hospital at Goodna.

The ninety-two patients who yielded worms after treatment had an average hemoglobin percentage of 73 per cent. of the normal by the Tallqvist scale. A representative series of 108 noninfected patients had an average hemoglobin percentage of 75. The ninety-two infected patients yielded an average of 19.3 hookworms each. Since they showed a reduction in their hemoglobin percentage below that of the noninfected controls of about 2 per cent. of the normal, the reduction was roughly 1 per cent. of the normal for ten worms harbored. These figures are only a rough estimate as the method of testing the hemoglobin could give only approximate results, and the number of observations was small.

The results of the preliminary examinations showed that 27.1 per cent. of the patients were infected with hookworms, that the average infection was light, and that most of the infection was contracted before the patients were transferred from the hospital at Goodna to the one at Sandy Gallop.

METHODS OF TREATMENT

Of the 121 patients found to be infected with hookworms, one was too ill to be treated and another developed a fatal attack of lobar pneumonia on the very day of receiving his first dose of the vermicide. The other 119 patients were divided into five groups of approximately twenty-four persons each, and the members of each group were treated according to one of the five methods given in detail in Table 1. The vermicides used were carbon tetrachlorid, oil of chenopodium and the two drugs in combination. Carbon tetrachlorid in doses of 3 c.c. had, in the previous work at Goodna, been found to be relatively so inefficient in removing *Ancylostoma duodenale* that no further tests were made of this drug in the same dosage.

There was no purging or starvation in preparation for treatment. The vermicides were given on an empty stomach, beginning at 6:30 a. m., and the midday meal was given in all cases at 12:30 p. m. The purge given after treatment always consisted of 45 gm. of magnesium sulphate in water. The oil of chenopodium and the carbon tetrachlorid were each given in about one fourth of a glass of water and drunk

quickly by the patient. The oil floated on the water and the carbon tetrachlorid sank to the bottom, but either was easily taken by this method, which is simpler than inducing insane patients to take drugs in capsules. When both drugs were given together to patients of Group 5 they were mixed just before administration and given with water as described. In the treatment of a few violent patients the use of the stomach tube was necessary.

METHODS OF EXAMINATION

All microscopic examinations were made by the Willis salt-flotation method.[2] A sample of feces filling about one sixth of a labeled cylindrical, quarter-ounce specimen tin was mixed with a saturated solution of common table salt. The mixture was stirred with a wooden toothpick, while the salt solution was added slowly until the tin was

TABLE 1.—*Plan of Treatments for Hookworm Infection and Methods Used*

Time of Treatment or Examination	Group 1: 24 Patients	Group 2: 24 Patients	Group 3: 23 Patients		Group 4: 24 Patients		Group 5: 24 Patients	
First day, 6:30 a.m. ...	1.5 c.c. oil of chenopodium	0.75 c.c. oil of chenopodium	5 c.c. carbon tetrachlorid		10 c.c. carbon tetrachlorid		0.75 c.c. oil of chenopodium, 5 c.c. carbon tetrachlorid	
8:30 a.m.	Purge	0.75 c.c. oil of chenopodium	A 12 patients	B 11 patients	A 12 patients	B 12 patients	A 14 patients	B 10 patients
10 a.m.	.....	Purge	Purge	.....	Purge	.....	Purge	.....
Second day, 6:30 a.m.	.....	.....	.....	Purge	.....	Purge	.....	Purge
First 72 hours.....	All stools examined for worms							
21st day.....	Feces of each patient examined by microscope (Willis method)							
22d day.....	All patients given 2 c.c. oil of chenopodium, in two doses one hour apart, and a purge two hours later							
Next 72 hours.....	All stools examined for worms							
42d day.....	Feces of each patient examined by microscope (Willis method)							
43d day.....	Patients still infected treated with 2 c.c. oil of chenopodium as before, and stools examined for 72 hours for worms							
Thereafter.....	Three weeks after each treatment the feces were examined microscopically and all patients still infected were treated with 2 c.c. of oil of chenopodium, as before, and the stools were examined for worms for 72 hours. This was continued until all were cured according to the microscopic tests							

just full. A clean, grease-free slide was then laid on the tin so that the surface of the mixture was in contact with the slide. After five or ten minutes the slide was raised and quickly turned over. The upper surface of the adhering pool of water was then examined for floating hookworm ova under the 16 mm. objective of the microscope. If no hookworm ova were found, the mixture in the specimen tin was again stirred and another slide applied. If the second preparation failed to show hookworm ova, their absence was recorded.

In examining stools for hookworms the method recommended by Darling, Barber, and Hacker was followed.[3] Every stool passed during

2. Willis, H. H.: A Simple Levitation Method for the Detection of Hookworm Ova, Med. J. Australia **2**:375-376 (Oct. 20) 1921.

3. Darling, S. T.; Barber, M. A., and Hacker, H. P.: Hookworm and Malaria Research in Malaya, Java, and the Fiji Islands; Report of the Uncinariasis Commission to the Orient, Rockefeller Foundation Pub. No. 9, 1920, p. 28-31.

seventy-two hours after treatment was collected and washed through a brass sieve of 60 meshes to the inch. The residue in the sieve was suspended in water in dark photographic trays, and the worms were picked out by painstaking systematic search. They were then put into hot 70 per cent. alcohol and set aside for closer identification later.

All the examinations after the first general examination of the institution were made by the same trained microscopist of the Hookworm Campaign. He lived at the hospital during the height of the work, and he planned the treatments so that there would be sufficient time for the numerous laborious worm counts required.

RELATIVE ACCURACY OF THE WILLIS SALT-FLOTATION METHOD AND WORM COUNTS

The Willis salt-flotation method had been shown by several investigators to be more delicate than the direct microscopic examination of water suspensions of feces or of the sediment obtained by centrifuging such suspensions. It had also been found to require less time and less apparatus than the centrifuge method. It remained to be ascertained how this method compared in accuracy with the search of stools for hookworms after a test treatment with an effective vermicide.

As has been shown in Table 1, three weeks after the first round of treatments all the patients in the treatment groups were examined both by the Willis method and by the administration of 2 c.c. of oil of chenopodium in a divided dose followed by search for hookworms in all stools passed during the subsequent seventy-two hours. This gave an excellent opportunity for a comparative evaluation of these methods of diagnosis.

That 2 c.c. of oil of chenopodium, as administered in these tests, should remove on an average over 96 per cent. of all hookworms present is suggested by the fact that Smillie [4] removed this percentage of worms by a divided dose of only 1.5 c.c. of oil of chenopodium given in the same way to a series of fifty-six infected persons. He tested his results against a subsequent dose of 3 c.c. of oil of chenopodium, divided into three parts given hourly. There was a preliminary purge the evening before this large test dose and another an hour and a half after the last administration of oil of chenopodium. This method of giving 3.0 c.c. of oil of chenopodium is said to remove on an average 99 per cent. of the hookworms present.[5] As this larger test dose is not infrequently followed by disconcerting symptoms, it seemed preferable

4. Smillie, W. G.: Studies on Hookworm Infection in Brazil, 1918-1920: Second Paper. Monographs of the Rockefeller Inst. for Med. Res., No. 17, May 12, 1922, p. 68.

5. Darling, S. T., and Smillie, W. G.: Studies on Hookworm Infection in Brazil: First Paper. Monographs of the Rockefeller Inst. for Med. Res., No. 14, Feb. 1, 1921, p. 4.

at Sandy Gallop to give 2 c.c. of oil of chenopodium in test treatments, even if this should necessitate a greater number of treatments and worm counts.

In testing the reliability of diagnoses of hookworm disease made by microscope in the field in Brazil, Darling and Smillie [6] administered a subsequent test treatment of 3 c.c. of oil of chenopodium by the method already described, and counted the hookworms expelled. The

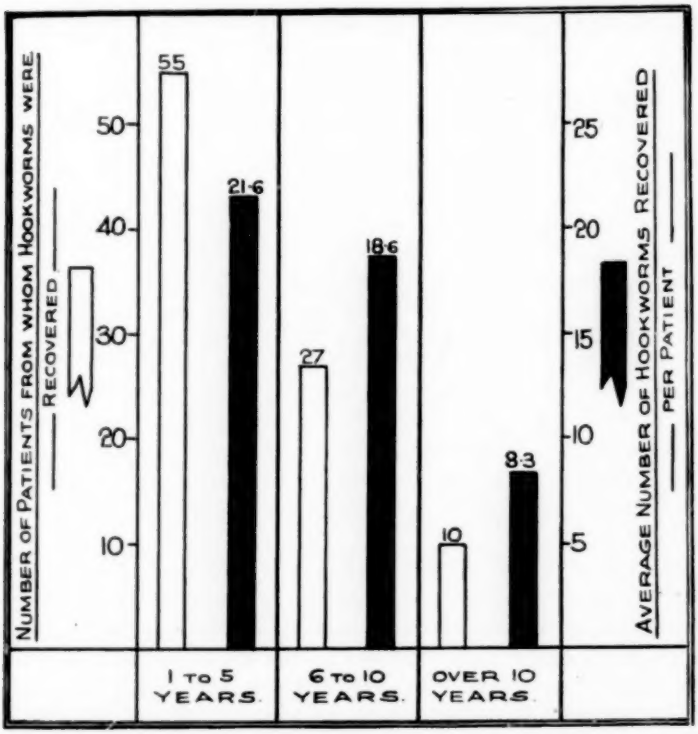

Fig. 1.—Relation of the length of stay in the hospital at Sandy Gallop to the number of hookworms harbored.

method which had been used in making the preparations for microscopic examination in the field is not stated, but it is assumed that water suspensions of the feces were centrifuged and examined before the specimens were declared negative, in accordance with the technic in common use in Brazil at the time. The results of these studies in Brazil led Darling and Smillie to the opinion that "The use of microscopic results as an index of the cure of hookworm disease after treat-

6. Foonote 5, pp. 14 and 15.

ment is of little value and gives a false sense of security." [6] That this opinion does not hold for the more delicate Willis method of microscopic diagnosis when tested against the search for worms expelled after the moderately less efficient test dose of 2 c.c. of oil of chenopodium, is shown in Table 2, in which the results at Sandy Gallop are shown and compared with those of Darling and Smillie in Brazil.

It is evident that the Willis method as applied at Sandy Gallop was more accurate as a diagnostic measure than the counting of the worms expelled after a divided dose of 2 c.c. of oil of chenopodium. The

TABLE 2.—*Comparisons of the Accuracy of Examination by Microscopic and Worm Count Methods*

	Methods Used at Sandy Gallop, Queensland	Methods Used in Brazil (after Darling and Smillie)
Examined by both methods	119	78
Found infected by either method	57	51
Found infected by microscope	55	28
Found infected by worm count	41	48
Percentage discovered by microscope	96.5	54.9
Percentage discovered by worm count	71.9	94.1

TABLE 3.—*Worms Recovered After Treatment*

Group	1	2	3	4	5	Total
Number of persons in group	24	24	23	24	24	119
Number of persons in group yielding hookworms	19	20	19	17	17	92
Ancylostoma duodenale: Males	80	151	128	146	113	618
Females	143	272	182	191	213	1 001
Total	223	423	310	337	326	1,619
Necator americanus: Males	33	0	3	18	1	55
Females	65	2	4	31	1	103
Total	98	2	7	49	2	158
Total number of hookworms	321	425	317	386	328	1,777
Average number of hookworms per person treated	13.4	17.7	13.8	16.1	13.7	14.9
Average number of hookworms per person yielding hookworms	16.9	21.3	16.7	22.7	19.3	19.3

greater reliability of the microscopic examinations in Sandy Gallop when compared with those investigated in Brazil is probably largely due to the advantage of the salt-flotation method over the centrifuge method, but it may be partly explained by the advantages of hospital conditions over routine field conditions, especially with regard to the possibility of interchanging specimens.

HOOKWORMS EXPELLED BY TREATMENT

Of the 119 patients included in the treatment groups, ninety-two yielded hookworms after one or more of their treatments. The number, species, and sexes of the worms removed are given in Table 3.

Ten times as many of the hookworms recovered were of the species *Ancylostoma duodenale* as of the species *Necator americanus*, doubtless because the hospital had been infected by hookworms brought from Goodna, where there was a long-standing institutional infection with *Ancylostoma duodenale*. The predominant hookworm of Queensland is *Necator americanus*. Only eight patients among the ninety-two yielded any hookworms of the species *Necator americanus*. In every case all the *Necator* worms were expelled by the first, or trial, treatment.

There were four patients who yielded over 100 hookworms: one patient in Group 1 expelled 103 hookworms, ninety-four of which were *Nectator* worms; two in Group 2 expelled 113 and 116 *Ancylostoma* worms, respectively; and one in Group 4 expelled 212 of the *Ancylostoma* species.

TABLE 4.—*Efficiency of the Methods of Treatment*

Vermicide of Trial Treatment	Group	Number of Persons	Cures After Trial Treatment as Shown by Microscopic Examination		Worms Recovered, Trial Treatments	Worms Recovered, Subsequent Treatments	Total Number of Worms	Percentage Removed, Trial Treatment
			Number	Percentage				
1.5 c.c. oil of chenopodium, single dose	1	24	9	37.5	248	73	321	77.2
1.5 c.c. oil of chenopodium, divided dose	2	24	17	70.8	393	32	425	92.5
5 c.c. carbon tetrachlorid	3	23	12	52.2	287	30	317	90.5
10 c.c. carbon tetrachlorid	4	24	15	62.5	370	16	386	95.8
0.75 c.c. oil of chenopodium with 5 c.c. carbon tetrachlorid	5	24	11	45.8	240	88	328	73.2
Total		119	64	53.8	1,538	239	1,777	86.6

EFFICIENCY OF THE METHODS OF TREATMENT

The efficiency of each of the five methods of treatment was measured in terms of cures and also of hookworms removed by the first or trial treatment. The results are given in Table 4.

The data in Table 4 permit the listing of the methods of treatment in the order of their efficiency as follows:

On basis of cures determined by the microscope (Willis method)
1. 1.5 c.c. oil of chenopodium in divided dose (Group 2)
2. 10 c.c. carbon tetrachlorid (Group 4)
3. 5 c.c. carbon tetrachlorid (Group 3)
4. 0.75 c.c. oil of chenopodium plus 5 c.c. carbon tetrachlorid (Group 5)
5. 1.5 c.c. oil of chenopodium in a single dose (Group 1)

On basis of percentage of hookworms removed (Fig. 2)
1. 10 c.c. carbon tetrachlorid (Group 4)
2. 1.5 c.c. oil of chenopodium in divided dose (Group 2)
3. 5 c.c. carbon tetrachlorid (Group 3)
4. 1.5 c.c. oil of chenopodium in a single dose (Group 1)
5. 0.75 c.c. oil of chenopodium plus 5 c.c. carbon tetrachlorid (Group 5)

The groups of patients were not large enough to give significance to moderate differences between the results from the several methods. The conclusions would seem justified, however, that under the conditions of the tests 10 c.c. of carbon tetrachlorid and the divided dose of 1.5 c.c. of oil of chenopodium were each more efficient than any of the other three methods; that 5 c.c. of carbon tetrachlorid came next in efficiency; and that the single dose of 1.5 c.c. of oil of chenopodium and the mixture of 0.75 c.c. of oil of chenopodium with 5 c.c. of carbon tetrachlorid were the least efficient. The previous work at Goodna had shown that doses of 3 c.c. of carbon tetrachlorid were not sufficiently effective to warrant their use in treating *Ancylostoma* infections as only 23.1 per cent. of the patients treated by this method were cured, and

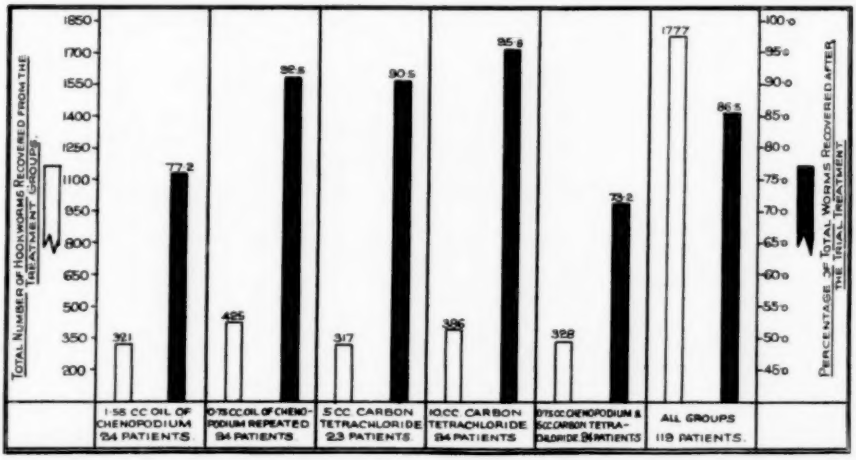

Fig. 2.—The total number of hookworms recovered from each treatment group and the percentage recovered after trial treatment.

the results were also very poor when measured by worm counts.[2] As the safety of carbon tetrachlorid in doses as large as 5 c.c. has recently been questioned and has not yet been definitely determined, the best method of those tested at Sandy Gallop for the routine treatment of infections with *Ancylostoma duodenale* would seem to be the divided dose of 1.5 c.c. of oil of chenopodium.

EFFECT OF THE PURGATIVE ON THE EFFICIENCY OF CARBON TETRACHLORID

The three groups of patients receiving carbon tetrachlorid were each divided into two subgroups, *A* and *B*, as shown in Table 1. Those in subgroup *A* received the purge 3.5 hours after the vermicide was

given, while those in subgroup *B* were given the purge on the morning of the following day. As shown in Table 5, the results following the early administration of the purge (Subgroups *A*) were the best in all cases, but the differences when carbon tetrachlorid was administered alone (Groups 3 and 4) were not large and may not be significant, considering the small series of observations. The difference was more striking when the mixture of oil of chenopodium and carbon tetrachlorid was given (Group 5), and may have been related to the overcoming of the slight laxative effect of carbon tetrachlorid by the constipating action of oil of chenopodium.

The laxative effect of carbon tetrachlorid was evident when 10 c.c. of the drug were administered without a purge: five of the twelve patients receiving this treatment had bowel movements within four

TABLE 5.—*Effect of the Purgative on the Efficiency of Carbon Tetrachlorid*

	Subgroup A				Subgroup B			
	Number of Patients Yielding Worms	Total Number of Hookworms Recovered	Worms Recovered, Trial Treatment	Percentage Recovered, Trial Treatment	Number of Patients Yielding Worms	Total Number of Hookworms Recovered	Worms Recovered, Trial Treatment	Percentage Recovered, Trial Treatment
Group 3 5 c.c. carbon tetrachlorid	10	86	82	95.3	9	231	205	88.7
Group 4 10 c.c. carbon tetrachlorid	9	279	270	96.8	8	107	100	93.5
Group 5 0.75 c.c. oil of chenopodium and 5 c.c. carbon tetrachlorid	10	299	231	77.3	7	29	9	31.0
All groups	29	664	583	87.8	24	367	314	85.5

hours, and eight, within six hours. When 5 c.c. of carbon tetrachlorid were given, only one of eleven patients had a bowel movement within four hours, and a total of seven had one within six hours. The mixture of carbon tetrachlorid with oil of chenopodium had no appreciable laxative effect; none of the ten patients receiving this medication had a bowel movement within four hours, and only two within six hours.

There would seem to be some advantage in giving a purgative after the administration of carbon tetrachlorid as a vermicide.

INQUIRY INTO THE SELECTIVE ACTION OF CARBON TETRACHLORID AGAINST FEMALE ANCYLOSTOMES

On learning of an unpublished observation that carbon tetrachlorid had a marked selective action against female worms in *Necator americanus* infections and differed in this respect from oil of chenopodium, the data collected at Sandy Gallop were analyzed to show the

efficiency of the treatments according to the species and sexes of the hookworms expelled. As all the necators were removed by the trial treatment, they had to be excluded from the comparisons. In Table 6 is shown the percentage of male and female ancylostomes removed by the first, or trial, treatment of each group of patients. It is apparent that, in this series, a slightly larger proportion of male worms than of female worms was removed by the first treatment in every case, and that the differences between oil of chenopodium and carbon tetrachlorid in their slight selective action against the male worms were too small and inconstant to be of significance.

SYMPTOMS FOLLOWING TREATMENT

There seemed to be little choice between the two drugs in the dosage used, so far as symptoms following treatment were concerned.

TABLE 6.—*The Selective Action of Carbon Tetrachlorid and Oil of Chenopodium Against Male Ancylostomes*

Group	Method of Treatment	Total Number of Ancylostomes Removed			Percentage Removed by Trial Treatment		
		Male	Female	Total	Male	Female	Total
1	1.5 c.c. oil of chenopodium, single dose	80	143	223	80.0	60.1	67.3
2	1.5 c.c. oil of chenopodium, divided dose	151	272	423	93.4	91.9	92.4
3	5 c.c. carbon tetrachlorid	128	182	310	92.9	88.5	90.3
4	10 c.c. carbon tetrachlorid	146	191	337	99.3	92.1	95.2
5	0.75 c.c. oil of chenopodium and 5 c.c. carbon tetrachlorid	113	213	326	76.1	71.4	73.0
All groups		618	1,001	1,619	89.8	82.4	85.2

The group showing the fewest symptoms was the one which received the smaller dose (5 c.c.) of carbon tetrachlorid. Doubtless more subjective symptoms would have been reported if the patients had been normal mentally. The symptoms observed are shown in Table 7.

As previously stated, one patient developed acute lobar pneumonia on the very day on which he had received his first treatment for hookworm disease. The vermicide used consisted of 0.75 c.c. of oil of chenopodium and 5 c.c. of carbon tetrachlorid, as given to Group 5. The patient was a demented man, 35 years of age, who had been admitted as having alcoholic mania. He died in the evening of the fourth day of his illness. Necropsy was performed by Dr. Morrison, superintendent of the hospital. Nothing of special interest was found beyond various stages of gray and red hepatization of the entire left lung and engorgement and early red hepatization of the lower and middle lobes of the right lung. The liver was not enlarged but appeared somewhat granular and light in color. There was cloudy swelling of spleen and kidneys. A specimen of tissue from the liver

was sent to Dr. J. V. Duhig, pathologist in Brisbane, and he reported that the cells of the lobules, more especially about the portal zone, appeared faintly cloudy with blurring of their nuclei, changes which might be due to the acute illness. No signs of fat necrosis were noted.

CONTROL MEASURES

At the conclusion of the investigation it was recommended that all patients before transfer from the hospital at Goodna to the one at Sandy Gallop be examined for hookworm disease, and cured if infected; that locked boots be worn by all patients who cannot otherwise be kept in boots while in the yards; that the strictest possible watch be

TABLE 7.—*Symptoms Observed After Treatment*

Group	Drug and Dose	Number of Patients: Treated	Vomiting	Feeling Sick	Appearing Drowsy	Comments
1	1.5 c.c. oil of chenopodium, single dose	24	6	0	0	
2	1.5 c.c. oil of chenopodium, divided dose	24	6	0	0	
3	5 c.c. carbon tetrachlorid	23	2	0	0	
4	10 c.c. carbon tetrachlorid	24	6	1	2	1 case of persistent vomiting for 48 hours
5	0.75 c.c. oil of chenopodium and 5 c.c. carbon tetrachlorid	24	6	1	1	
Test treat.	2 c.c. oil of chenopodium, divided dose	119	17	2	0	1 case of persistent vomiting for 48 hours

maintained to keep the yards free from soil pollution, and that the patients be examined yearly for hookworm infection and treated if infected.

CONCLUSIONS

1. In doses at present regarded as sufficiently safe for use on a large scale in the field, carbon tetrachlorid is not as efficient as oil of chenopodium in the treatment of infections with hookworms of the species *Ancylostoma duodenale*.

2. Oil of chenopodium in a dose of 1.5 c.c., given in two equal parts at an interval of two hours and followed by a purge, proved highly efficient and was superior to the undivided dose.

3. The Willis salt-flotation technic of microscopic examination of feces is a simple and efficient test of the presence of hookworm infection, and compares well, as a method of determining cures, with the search for hookworms expelled after safe doses of oil of chenopodium.

4. Carbon tetrachlorid is a mild laxative, but it cannot be depended on to move the bowels when used in moderate doses or mixed with oil of chenopodium. It would seem good practice to give a purge three or four hours after the administration of this drug.

CLINICAL RESULTS OBTAINED WITH BACILLUS ACIDOPHILUS *

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Bacillus acidophilus has been used successfully in the treatment of constipation and diarrhea.[1] However, it would be difficult to state precisely how successful a therapeutic agent it is. Neither of the intestinal conditions dealt with—constipation and diarrhea—permit exact definition; consequently, the interpretation of results must be somewhat arbitrary. For this reason, if no other, it would seem desirable that investigators in this field present their facts as objectively as possible. Obviously, there are many factors which must be considered. The necessity for keeping a careful record of the frequency and character of defecations is well recognized. The dosage of *B. acidophilus* preparations is always of importance, but unfortunately it is unstandardized and therefore at present has little significance. Thus 10 c.c. of *B. acidophilus* milk containing 20,000,000 viable organisms per cubic centimeter in the hands of one clinician is unquestionably more desirable than 1,000 c.c. containing 10,000 viable organisms per cubic centimeter when administered by another. Since the transformation of the intestinal flora from the proteolytic to the aciduric type appears to depend on a mass inoculation, the importance of ingesting large numbers of viable *B. acidophilus* cannot be overemphasized. It is common experience that frequently in treating severe cases of chronic constipation it is necessary to increase the dose before obtaining beneficial results. We have given as much as 1,500 c.c. of *B. acidophilus* milk and 400 gm. of lactose daily in some instances before alleviating the constipated condition. Another practice that has proved valuable in difficult cases is the use of a high enema of *B. acidophilus* milk, thinned with a small amount of warm water. Generally these enemas are advised on two or three successive days. It is likely that in cases reported as failures, a sufficient increase in the number of viable organisms administered might have resulted in success. In this connection it may also be stated that the chief criticism against the commercial preparations of *B. acidophilus* now on the market is that the number of viable organisms they contain is too small to yield satisfactory results when compared with the mass inocu-

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1. Kopeloff, N.: Is the Action of *Bacillus Acidophilus* a Strictly Bacteriologic Phenomenon? J. A. M. A. **80**:602-604 (March 3) 1923. Rettger, L. F., and Cheplin, H. A.: The Intestinal Flora, Yale University Press, 1921.

lations made by scientific investigators. It is unfortunate, therefore, that the commercial products examined cannot bear recommendation.

It is not only important to study the influence of *B. acidophilus* on the intestinal condition as compared with the period immediately preceding treatment, but also to note how long any changes which have been induced persist. In previous communications these facts have been indicated, and the present report is concerned with the continuation of such an investigation. The female psychotic patients under treatment for constipation were twenty-seven in number, in addition to which there were also three mentally normal subjects. Two more subjects, one of them psychotic, were under treatment for diarrhea. The procedure and technic have been described elsewhere. The *B. acidophilus* milk which was administered varied from 110,000,000 to 440,000,000 viable organisms per cubic centimeter, with an average of about 200,000,000 per cubic centimeter. Recent radiographic examination to determine intestinal motility in some of the patients caused them to be divided into two equal groups showing atonic and spastic constipation.

In Table 1 are included the results of the treatment of constipation and diarrhea with *B. acidophilus* milk. It will be seen that this table has been so arranged as to show three periods: Before treatment, during treatment and after treatment. Under each period there are two columns, the second showing the number of days of observation, the first showing the number of days during which the normal defecations occurred. More than one normal defecation per day has been counted as only one defecation so as not to confuse the main consideration. The period after treatment has been divided into two parts: the first, to show the effect of continuing the ingestion of lactose alone; the second, comparable to the period before treatment. The final column of "Remarks" indicates the reasons for discontinuing treatment. Whenever this is blank, it is to be understood that observations are being continued.

If the data for patients 1 to 7 are examined in some detail, it will be seen that without exception there has been a significant increase in the number of defecations during treatment with *B. acidophilus* milk and lactose as compared with the period before treatment. In several instances this is striking, when the severity of the constipation is considered. Thus patients 1, 3, 4 and 6 had one defecation per week or less before treatment and three or more defecations per week during treatment. Patients 1, 2 and 5 had almost daily defecations during treatment. Patient 8 was disturbed throughout the treatment, frequently refusing and sometimes spilling the milk. She has failed to respond to treatment which has not been as intensive as desired. While it is not feasible to include all the data concerning the amount

and character of the feces of the patients under observation, in almost every instance there has been recorded an increase in the amount of feces as well as a change in color and consistency. The feces usually became lighter in color and much softer in consistency. Patients 9 to 12 are of special interest since they have been given lactose alone following the period during which they received *B. acidophilus* milk

TABLE 1.—*The Influence of B. Acidophilus Milk on Constipation and Diarrhea*

		Before Treatment		B. Acidophilus Milk + Lactose		After Treatment: Lactose		After Treatment: Nothing		
Number	Name	No. of Normal Defecations	Number of Days	No. of Normal Defecations	Number of Days	No. of Normal Defecations	Number of Days	No. of Normal Defecations	Number of Days	Remarks
1	K. Hy.	2	14	51	62	..	..	22	38	Too disturbed
2	M. Ky.	17	73	59	61	..	..	195	270	Paroled
3	L. R.	11	103	13	27	..	..	226	341	
4	M. Cn.	0	7	52	160	..	..	42	61	Paroled
5	M. Hy.	95	116	28	39	..	..	133	137	Paroled 100 days
		3	27	1	7	..	..	..	..	Continued
6	S. Fz.	1	34	67	99	..	..	24	84	Discontinued
		0	10	34	49	..	..	..	..	Continued
7	S. Sr.	12	19	16	18	..	..	129	169	Paroled
8	R. Sn.	12	18	32	61	..	..	40	100	Too disturbed
9	C. Et.	8	31	41	62	57	70	34	37	Childbirth
10	M. Et.	1	7	47	50	74	124	2	44	
11	R. Rr.	4	28	17	22	56	60	3	6	
						12	14	..	..	Paroled
12	M. Hn.	49	92	109	189	57	119	29	54	
13	M. Fd.	1	14	55	101	..	..	..	..	Illness
14	M. Hw.	1	12	26	48	..	..	..	..	Paroled
15	K. Rb.	0	14	93	175	..	..	..	..	Continued
16	M. Fx.	2	25	16	22	..	..	..	..	Paroled
17	A. Dz.	5	47	42	86	..	..	..	..	Paroled
18	E. Sh.	21	64	5	7	..	..	..	..	Too disturbed
19	E. Bt.	19	45	17	49	..	..	..	..	Continued
20	E. Hb.	2	7	14	17*	..	..	27	39	
21	A. Hn.	1	6	7	18*	..	..	6	27	Too resistive
22	C. Sn.	3	7	41	49*	..	..	..	..	Continued
23	I. Gr.	3	15	42	61*	..	..	..	..	Continued
24	A. Br.	3	15	30	62*	..	..	..	..	Continued
25	B. Sn.	3	27	6	14*	..	..	..	..	Continued
26	S. Shr.	0	28	0	14*	..	..	..	..	Continued
27	A. Sy.	0	16	5	14*	..	..	..	..	Continued
				Normal Subjects—Constipation						
28	M. Wr.	5	30	53	56	66	66	89	89	
29	H. Wn.	4	30	106	120	..	..	43	64	
				46	46	..	..	..	..	Continued
30	J. Hn.	8	14	28	28	..	..	7	7	
				Diarrheal Subjects						
31	M. Kz.	234	39	37	23	..	..	..	..	Discontinued
32	W. Kt.	135	27	74	36	..	..	..	..	Discontinued

* B. acidophilus milk but no lactose.

and lactose. This was done in order to determine whether the beneficial effects of *B. acidophilus* could be prolonged by supplying carbohydrate in sufficient quantity for bacterial development. It will be seen that Patient 9 had forty-one defecations in two months while receiving *B. acidophilus* and lactose, and on lactose alone she had fifty-seven defecations in a slightly longer period, indicating that the beneficial effect persisted for at least this length of time. For a little over a month following this, during which feeding of lactose was stopped,

this patient continued to have almost daily defecations as compared with eight defecations per month in the period of observation preceding treatment. Patient 10, who had only one defecation in the week preceding treatment and then had forty-seven defecations in fifty days while receiving *B. acidophilus* and lactose, continued favorably for four months when taking lactose alone. However, when the lactose administration was discontinued, she became severely constipated again. Practically the same course was run by Patient 11. Patient 12 usually responded to treatment, although the figures here presented, 109 defecations in 189 days while receiving *B. acidophilus* and lactose, do not indicate that for the last two months of this six month period she had fifty-seven defecations in sixty-four days. However, when *B. acidophilus* was discontinued, a retrogression to her original condition occurred. From an analysis of these few cases it seems likely that the beneficial effects of *B. acidophilus* treatment can be prolonged by the use of lactose, even after the ingestion of viable organisms has stopped. The alternative explanations thus suggested are: first, that the lactose furnishes a suitable medium for the development of *B. acidophilus* in the intestine and perpetuates the transformation of the intestinal flora; or second, that the lactose alone is responsible for the relief of constipation. While it is generally accepted that lactose has laxative properties, nevertheless its use has never been accompanied by such uniformly good results as have been obtained with *B. acidophilus*. In order to obtain further data along these lines, there has been included in Table 1 a series of Patients 13 to 19 who have received *B. acidophilus* milk and lactose as against another series—20 to 27—who have received *B. acidophilus* alone. Patients 13 to 18 showed a striking increase in the number of defecations while receiving *B. acidophilus* milk and lactose as compared with the period before treatment. Thus, Patients 13 to 17, who had about one normal defecation in two weeks before treatment, had a defecation every other day after treatment. Patient 19 is still receiving treatment because of her failure to respond. As might be expected the normal subjects, 28 to 30, yielded results identical with those obtained with psychotic patients. Patients 20 to 27 have received *B. acidophilus* milk without lactose. Here again there is a striking increase in number of defecations during treatment as compared with the preceding period of observation. The last three patients—25 to 27—have received treatment only two weeks and therefore cannot be expected to show such marked improvement. A comparison between the patients receiving *B. acidophilus* milk and lactose and those receiving lactose alone leads to the conclusion that the beneficial effect of *B. acidophilus* treatment depends rather on the viable organisms than on the laxative properties of the lactose. In fact, Rettger and Cheplin in their comprehensive investigation have estab-

lished the relative value that attaches to the feeding of *B. acidophilus* with and without different sugars, and these data corroborate their findings.

There remain the diarrheal subjects still to be considered. The first of these, Patient 31, was psychotic. She averaged approximately six defecations a day. All medical efforts to alleviate her condition were without avail. On treatment with *B. acidophilus* milk without lactose the number of defecations was greatly reduced, and for the last week of treatment she had only one defecation a day. The other subject, No. 32, presented a similar condition in lesser degree, and was soon benefited.

One of the most important questions which arises in connection with the therapeutic value of *B. acidophilus* is whether the relief obtained from constipation and diarrhea is permanent or merely transitory. From the data presented in Table 1 there is no doubt that the beneficial effects of *B. acidophilus* are in evidence so long as the treatment is in progress. However, if attention is directed to the period following treatment when neither *B. acidophilus* nor lactose was ingested some interesting facts are disclosed. With the exception of two cases, those of Patient 8, who never fully responded to treatment, and Patient 12, the number of normal defecations in the period following treatment has been greater than in the period before treatment. The length of time of the period following treatment is of significance in interpreting these results. It has varied from six to 341 days. For a period of less than three months following treatment the beneficial effects have persisted in all but one instance. The cases of the four patients who have been observed for more than four months following tretament are worthy of a detailed account. Patient 2 has had 195 defecations in 270 days following treatment. During the thirty days preceding the writing of this paper this patient had twenty-seven normal defecations eight months after treatment. However, it must be mentioned that the amount of feces excreted has diminished perceptibly, so that this patient has been advised to take lactose. Patient 3 has had 236 defecations in 341 days following treatment, as compared with eleven in 103 days preceding treatment. During thirty days, nine months after treatment, she had sixteen defecations. Patient 5 had 133 defecations in 137 days following treatment, as compared with ninety-five defecations in 116 days preceding treatment. Following a gynecologic operation and her parole of three months, she became severely constipated. The last subject, Patient 7, had 129 defecations in 169 days following treatment, twenty-three in the thirty days preceding the writing of this paper.

In general, then, it may be stated that the beneficial effects of *B. acidophilus* have persisted for a considerable period of time sub-

sequent to treatment; in fact, for more than eleven months. However, it must be recognized that there is a perceptible tendency toward diminution in the amount of feces excreted. This might be favorably influenced by the continued use of lactose, as has been indicated. Thus, the improvement in Patients 9, 10, 11 and 12, who took lactose from two to four months following the ingestion of *B. acidophilus* was retained in a satisfactory manner.

TRANSFORMATION OF INTESTINAL FLORA

The transformation of the intestinal flora is an important consideration in *B. acidophilus* therapy. As has been already stated, a weekly microscopic examination of the feces has been made, and the relative percentage of gram-positive and gram-negative bacteria recorded. Further, the feces have been plated on whey agar and the percentage of *B. acidophilus* colonies reported. Because of the space that would otherwise be required, these data have been summarized in Table 2. A final column has been added showing the number of days during which one or more normal defecations occurred in the thirty days subsequent to the time the bacterial counts indicated were made. It should be stated that the highest percentage of gram-positive bacteria generally occurred simultaneously with the highest percentage of *B. acidophilus* colonies on the plates, but this was not invariably the case. The number of defecations is recorded for the thirty days following the highest microscopic count of gram-positive organisms.

There are several interesting facts revealed in Table 2. The most important of these is that the highest percentage of gram-positive bacteria in the feces is an almost certain index that the number of normal defecations will be highly satisfactory subsequently for at least thirty days. Thus, with the exception of Patient 6, who received no treatment following the highest count; Patient 8, who was too disturbed to react favorably, and Patient 27, who in twenty days failed to respond to treatment, all of the cases averaged two or more defecations in three days. Many of these had almost daily defecations. It should be remembered that most of these patients suffered from severe constipation prior to treatment. (Twelve of the twenty-two patients recorded had one defecation or less per week, and the remainder did not have many more.) These figures point directly toward the conclusion that the transformation of the intestinal flora is responsible for the improvement of the patients under consideration. A detailed examination of the data in Table 2 again shows that the highest microscopic counts of gram-positive bacteria fall considerably below 100 per cent. In fact, 85 per cent. is the highest figure recorded. About two thirds of the counts are above 50 per cent., as compared with an average count of about 16 per cent. of gram-positive bacteria before

treatment. The microscopic counts and the plate counts are not in good agreement, for in half the cases the microscopic count is higher than the plate count, and vice versa, due to the presence of dead bacteria in the microscopic count. It is interesting, however, to note the condition of the patients showing 100 per cent. of *B. acidophilus* in their feces, namely, Patients 13, 22, 23 and 24. The first three of these had practically daily normal defecations, while the last did not respond so perfectly to treatment. This again indicated that a transformation of the intestinal flora to the aciduric type is responsible for an increase in the number of normal defecations. It is of interest in this connection to mention again the fact that in three patients, namely,

TABLE 2.—*Relative Percentage of Gram-Positive Bacteria in Feces*

Number	Name	Highest Percentage of Gram-Positive Bacteria: Microscopic Percentage	Highest Percentage of Gram-Positive Bacteria: Plate Percentage of B. Acidophilus	Number of Normal Defecations for Succeeding 30 Days
1	K. Hy.	53	94	26
2	M. Ky.	68	*	30
3	L. Rh.	78	*	27
4	M. Cn.	35	7	22
5	M. Hy.	64	70	29
6	S. Fz.	80	50	11**
7	S. Sr.	37	4	26
8	R. Sn.	70	80	14
9	C. Et.	85	85	25
10	M. Et.	62	50	23
11	R. Rr.	78	11	30
12	M. Hn.	52	50	29
13	M. Fd.	85	100	28
14	M. Heu.	48	98	21
15	K. Rb.	85	65	20
16	M. Fx.	39	15	11 in 17 days
17	A. Dz.	70	3	13
18	E. Sh.	16	*	5 in 7 days
19	E. Bt.	Record incomplete		
20	E. Hh.	Record incomplete		
21	A. Hn.	Record incomplete		
22	C. Sn.	54	100	16 in 17 days
23	I. Gr.	43	100	28
24	A. Br.	37	100	15
25	B. Sn.	Record incomplete		
26	S. Shr	Record incomplete		
27	A. Sy.	34	0	6 in 20 days

* Not counted. ** Discontinued treatment.

Patients 3, 5 and 12, there were recovered from the feces viable *B. acidophilus* in considerable number six months after treatment had been discontinued.

COMMENT

Any interpretation of the results of this investigation must take into consideration its inherent difficulties. As stated at the outset, a discussion of constipation involves arbitrary standards. While the number of subjects has been limited, the effort has been made to study them in such a way as to make comparisons valid. In any event, the obvious benefits obtained by the use of *B. acidophilus* in cases of constipation and diarrhea can scarcely be questioned. A discussion of the mechanism of its action is reserved for another communication.

SUMMARY

1. A series of thirty constipated subjects were under observation before, during and after treatment with *B. acidophilus*. A comparison of these periods shows that during treatment the number of normal defecations was significantly increased.

2. The beneficial influence of *B. acidophilus* usually persists for a considerable period of time after treatment has been stopped. Patients have been observed for from one week to about one year after treatment, and almost without exception all have had more normal defecations after than before treatment.

3. The use of lactose during and after ingestion of *B. acidophilus* does much to enhance the beneficial effects.

4. A transformation of the intestinal flora from a proteolytic to an aciduric type as shown by microscopic and plate counts may generally be induced. Such transformation is usually accompanied by almost daily defecations regardless of the severity of the constipation.

5. Two cases of diarrhea have been successfully treated by the ingestion of *B. acidophilus*.

STUDIES ON THE NATURE OF BACILLUS ACIDOPHILUS THERAPY *

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The relief obtained from constipation and diarrhea by the use of *B. acidophilus* has been interpreted in several ways. In previous communications [1] it has been shown that the action of *B. acidophilus* milk is neither strictly physical nor chemical, that is, does not depend upon volume or chemical constituents, but appears to be essentially a bacteriologic phenomenon. This conclusion was based on the fact that neither sterile skim milk nor sterilized *B. acidophilus* milk influenced constipation, as did *B. acidophilus* milk in which the viable organisms were uninjured. The foregoing experiments were open to some criticism on the ground that sterilizing *B. acidophilus* milk caused a change in chemical composition. This study was therefore extended along somewhat different lines.

In order to feed *B. acidophilus* milk in which the viable organisms were eliminated, the following procedure was adopted: *B. acidophilus* milk prepared in the usual way was centrifuged, and the supernatant liquid was put through a Mandler diatomaceous filter. The labor involved was time consuming. It was through the courtesy of Dr. Charles Krumwiede, assistant director of the Research Laboratories of New York City Health Department, that we were able to use a Sharpless supercentrifuge, which greatly facilitated the preliminary work. The liquid was then run through a "Vaccu-Filter," a coarse Mandler diatomaceous filter, and finally through a fine Mandler filter. This filtrate was always tested for sterility on whey agar plates and was fed to patients as "bacillus acidophilus filtrate," 900 c.c. per day. This amount is roughly equivalent to the liquid portion of 1,000 c.c. of regular *B. acidophilus* milk. An attempt was made to feed the residue from the supercentrifuge which contained viable *B. acidophilus* organisms, for comparison with the filtrate; but, unfortunately, the supply was not continuous, and therefore the results were inadequate. In stating in our previous communication the results of feeding sterilized *B. acidophilus* milk, mention was made of the fact that the acidity of *B. acidophilus* milk was neutralized prior to sterilization. This procedure obviously affected the lactic acid content. Consequently, in

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continuing the feeding of sterilized milk in the present study, chemically pure lactic acid was added to sterilized *B. acidophilus* after sterilization in an amount equivalent to the acidity as previously titrated by twentieth normal sodium hydroxid. In accordance with the general plan of our *B. acidophilus* studies, the subjects were psychotic patients, numbers thirty-five to thirty-eight being male and the others female. Observations as to daily defecations were recorded prior to treatment.

In Table 1 are presented the results as obtained with *B. acidophilus* milk prepared in the manner described above. Considering first the influence of "*B. acidophilus* filtrate" on constipation, it will be seen that in general there is little, if any, difference in the relative number of normal defecations in the period during which *Bacillus acidophilus* filtrate was ingested as compared with the period before treatment.

The Influence on Constipation of B. Acidophilus in Various Forms

		Before Treatment		Sterilized Bacillus Acidophilus Milk + Lactic Acid		Bacillus Acidophilus Filtrate		Bacillus Acidophilus Milk	
Number	Name	Number of Daily Defecations*	Number of Days	Number of Daily Defecations	Number of Days	Number of Daily Defecations	Number of Days	Number of Daily Defecations	Number of Days
25	B. Sn.	2	25	..	..	1	21	9	21
27	A. Sy.	0	15	..	..	2	21	6	21
33	K. Sa.	11	31	..	..	5	14	..	..
34	M. Bt.	0	5	..	..	0	13	..	..
6	S. Fz.	5	35	2	14	6	36	13	24
19	E. Bt.	12	35	6	21	16	38	7	23
35	E. Cy.	6	19	8	21	8	22	10	21
36	S. Ms.	13	21	17	21	16	22	19	22
37	A. Jn.	5	17	14	21	..	..	17	13
38	H. Gn.	6	17	9	21	..	..	11	21
79	J. Qn.	10	16	16	21	..	..	12	21

* Normal.

This is to say, that the chemical constituents of *B. acidophilus* milk, including the acid reaction, are not effective in alleviating constipation. Neither does the physical factor of volume exert much influence, since the patients received 900 c.c. of *Bacillus acidophilus* filtrate daily. The patients were subsequently given regular *B. acidophilus* milk, and it will be seen that with one exception all patients showed some increase in the number of normal defecations. This is not as striking as might perhaps have been anticipated, but it must be remembered that the patients had been permitted to become extremely constipated before obtaining *B. acidophilus* milk. Furthermore, the beneficial effects of *B. acidophilus* are ordinarily greatly enhanced by lactose which was not given in the present instance in order to avoid complicating the interpretation of results. These data, therefore, lend further support to the conclusion that *B. acidophilus* therapy is more strictly bacteriologic than it is chemical in nature. It is manifest that any bacteriologic phenomenon may be regarded as biochemical in character, and conse-

quently that of *B. acidophilus* is no exception. We have tried to determine where the chief emphasis belongs. Are the laxative qualities of *B. acidophilus milk* due mainly to the physical factor of volume? We have shown that this is not the case. Are they due to the chemical constituents elaborated by bacteria? These experiments would tend to disprove that contention. Are they due chiefly to the transformation of the intestinal flora as here indicated, and therefore essentially bacteriologic in nature? Further evidence of this may be found in data presented elsewhere, namely, that the beneficial effects of *B. acidophilus* persist for a considerable period of time after discontinuing treatment. Also it is important to note that viable *B. acidophilus* organisms have been recovered from the feces of patients six months after discontinuing treatment.

Again, when the results of feeding sterilized *B. acidophilus* to which lactic acid has been added, are considered, it will be seen that there is little evidence of any relief of constipation during this period as compared with the period before treatment. The physical factor of an increased volume was present of course. However, when regular *B. acidophilus* milk was added to the diet, in all but one instance an increase in the number of normal defecations was noted. While this increase is not striking, when all the facts are surveyed they again indicate that it is a bacteriologic rather than a chemical interpretation that will account for the action of *B. acidophilus*.

It has been shown how *B. acidophilus* affects elimination from the human intestinal tract, but the reason for this is a more difficult problem. The results here reported are to be regarded rather as suggestive than as final, since the studies are still in progress. However, there seems to be a sound basis for considering that *B. acidophilus* therapy is essentially bacteriologic in nature.

SUMMARY

1. In order to study the influence of physical and chemical factors, *B. acidophilus* milk was centrifuged and run through a Mandler diatomaceous filter. Thus the chemical constituents were little altered. When fed to constipated patients it was practically without effect. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations.

2. *B. acidophilus* milk was sterilized and lactic acid added, thus again approximating the original chemical composition. When fed to constipated patients, little change was noted. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations.

3. These data indicate that *B. acidophilus* therapy is essentially bacteriologic rather than physical or chemical in nature.

DISTURBANCES OF RENAL FUNCTION IN PERNICIOUS ANEMIA *

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In pernicious anemia there is frequently evidence of mild renal damage, manifesting itself by albumin, casts or both in the urine. Up to the present time it has been assumed that this renal irritation or damage is a result of malnutrition and anoxemia of the kidneys because of the anemia. On the other hand, the incidence of albuminuria and other clinical evidence of renal disturbance is low in cases of secondary anemia. The hemolytic intoxication of pernicious anemia may also injure the kidneys directly, but it has long been known that in pernicious anemia there is a superabundance of "free" or inorganic ionizable iron in the blood and tissues. That the deposition of iron in the kidneys may cause mild nephritic changes in experimental animals was demonstrated several years ago.[1] The presence, therefore, of renal hemosiderosis might be responsible for the renal disturbance in pernicious anemia. It was with this in mind that the following investigation was undertaken. The problem will be discussed along the following lines: the incidence of renal damage in pernicious anemia; its clinical and functional characteristics; the pathologic nature of this renal disorder, especially the presence, nature and degree of renal hemosiderosis; the effect of the deposition of iron in the kidney on renal function; and lastly, the correlation of these data.

The incidence of renal disturbance of a mild degree in pernicious anemia is high. Cabot [2] gives a 46 per cent. incidence of albuminuria in 506 cases of pernicious anemia. In fifty cases which have now been compiled from the records of Johns Hopkins Hospital, thirty-one, or 62 per cent., showed urinary albumin, casts, or both. In 100 cases from the Presbyterian Hospital, Chicago, 57 per cent. gave the same indication of renal impairment. The average incidence in these several groups is 50 per cent. On the other hand, in 100 cases of secondary anemia associated with a great variety of diseases from the Presbyterian Hospital, Chicago, albuminuria was present in only 14 per cent. And of these fourteen, four had nephritis or lesions of the urinary tract which were major factors in producing the anemia. The difference in the occurrence of albuminuria in the two types of anemia is striking.

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1. Stieglitz: Am. J. Anat. **29**:33, 1921.

2. Cabot in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger **4**, 628.

The average age of patients suffering from pernicious anemia with albuminuria is the same as for those without, but the group showing albuminuria show, on the average, a lower hemoglobin percentage than the group with negative urine findings. The average hemoglobin content of the blood for the 150 cases of pernicious anemia was 41 per cent., the average of the albuminuric cases was 36 per cent. and for those without albumin 46 per cent. The significance of this fact will be discussed later.

The clinical character of the renal disturbance has been studied by many, notably Christian,[3] Mosenthal[4] and Tileston and Comfort.[5] As far back as 1898 Albutt[6] described a rather fixed, low urinary specific gravity in connection with this disease. Essen and Porges[7] report twelve cases of pernicious and secondary anemia in which the renal disturbance became severe when the hemoglobin of the blood fell below 30 per cent.; the kidneys then functioned with a minimum of effort. Christian,[8] working with the Mosenthal[9] modification of the dietary test for renal function first suggested by Hedinger and Schlayer[10] studied the renal function in fourteen cases of pernicious anemia. He found that the renal function as evidenced by the ability of the kidney to concentrate the urine and respond to diuresis was similar to that found in chronic nephritis. The fixation of the urinary specific gravity was most marked when the hemoglobin was low, and if the anemia had persisted for a long time permanent renal impairment might occur. Christian suggested that this disturbance of the ability of the kidney to concentrate the urine was due to the anemia, and depended on nutritional deficiency or toxic disturbance. The phenolsulphonephthalein secretion was found to be about normal. This finding was confirmed by others. Mosenthal[11] gave exactly similar findings with the test that bears his name. On the other hand, Cabot[12] makes no mention of renal disorder in his studies of pernicious anemia.

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11. Mosenthal: J. A. M. A. **67**:933 (Sept. 23) 1916.
12. Cabot: Am. J. M. Sc. **120**:139, 1900.

Urobilin in increased quantities in the urine has frequently been described. The mechanism of the formation of urobilin is still in doubt,[13] but it is increased in any disease in which hemolysis is exaggerated.[14] Kahn and Barsky[15] report that there is relatively little alteration in the phenolsulphonephthalein test of Rountree and Geraghty.[16]

Our own results confirm these findings in six cases studied by the Mosenthal test, while eighteen phenolsulphonephthalein tests gave an average secretion of 65 per cent. of the dye in two hours. As Christian[8] points out, the fixation of the specific gravity and the increase of the night over the day volume of urine was noted as being most marked in the cases with the most marked anemia. The only abnormal finding in the blood chemistry of these cases was a uniform but slight increase in the uric acid content. The average in five cases was 4.2 mg. per 100 c.c. of blood, varying from 3.96 to 4.42. The nephritis of pernicious anemia is rarely, if ever, of such a degree as to be a marked factor in the prognosis.

The significance of the fixation of the specific gravity and the retardation of water elimination is particularly important in connection with the effects of iron deposition in the renal cells as discussed in a previous paper[1] and further elaborated in this.

The pathologic aspect of the renal changes of pernicious anemia that have been described clinically, is not so clear. No uniform pathologic changes are found grossly in the kidney at necropsy. In the protocols from the pathologic laboratory, Johns Hopkins Hospital, of necropsies of thirty-six cases of pernicious anemia, 83 per cent. of the cases showed a renal pathologic condition. The most common and uniform finding was tubular degeneration, often fatty in character, which occurred in 53 per cent. of all the cases. In 42 per cent. of the cases there was a gross renal hemosiderosis. The presence or absence of iron was not mentioned in the protocols of 44 per cent. of the cases, as no special search was made for iron at the time. The actual incidence of slight or microscopic hemosiderosis must be higher, especially in

13. Bauman, L.: Chemistry and Clinical Significance of Urobilin, Arch. Int. Med. **28**:475 (Oct.) 1921. Mueller: Ztschr. f. klin. Med. **12**:45, 1887; Kong. f. inner. Med. **11**:118, 1892.

14. Schneider, J. P.: Anemia, Arch. Int. Med. **17**:32 (Jan.) 1916; Study of Bile Pigments in Pernicious Anemia, J. A. M. A. **74**:1759 (June 26) 1920.

15. Kahn and Barsky: Chemistry of Pernicious Anemia, Arch. Int. Med. **23**:334 (March) 1919.

16. Rowntree and Geraghty: J. Pharmacol. & Exper. Therap. **1**:597, 1909. Rowntree, Fitz and Geraghty: The Effects of Experimental Chronic Passive Congestion of Renal Function, Arch. Int. Med. **1**:121 (Feb.) 1913.

view of our finding this condition in fourteen of fifteen cases. The protocols of twenty-five cases of pernicious anemia in which necropsy was performed at the University of Pennsylvania, showed that chronic parenchymatous nephritis was found in 36 per cent. and fatty changes in 24 per cent. From these data no far-reaching conclusions may be drawn, but one can say that the most characteristic change in the kidney of pernicious anemia is parenchymatous, tubular degeneration.

The second, and probably more important, finding is the renal hemosiderosis. In the series mentioned it was noted grossly in 42 per cent. of the cases. Warthin [17] reports a series of eight cases of pernicious anemia carefully studied, in all of which he found renal hemosiderosis. He concludes that the iron is deposited en route to excretion. Nothnagel [18] stated that the kidneys are usually pale, but often show a coffee brown color by transmitted light; he also described fatty changes and iron granules in the cells of the convoluted tubules.

Since Menghis in 1746 first found iron to be a constituent of the blood, iron metabolism and the distribution of the element has been much studied. Wells [19] gives a very complete summary of the chemical changes in the blood and tissues in pernicious anemia. Erben [20] states that in pernicius anemia the blood proteins are decreased, both in the serum and corpuscles, but are increased per corpuscle. The proportion of water is much increased in the blood. Cholesterol is decreased in the total blood, but is increased proportionally in the corpuscles. The total iron of the blood is less than normal because of the great reduction of the number of erythroplastids, but the serum contains more than the normal amount of iron. The proportion of iron per corpuscle is also increased, as indicated by the high color index so characteristic of pernicious anemia. Erben further states that the concentration of iron in the erythroplastids is greater than the concentration of hemoglobin would warrant, and he concluded that either the hemoglobin was particularly rich in iron, or that iron was present in some other form. Rumpf [21] confirms these analyses of Erben and adds that there is an increased sodium chlorid content of the tissues, associated with a marked poverty of potassium. Fowell [22] again confirmed the finding of an excess of free iron in the blood. That there is an increased elimination of iron in the urine has been shown by Kennerknecht,[23]

17. Warthin: Am. J. M. Sc. **124**:674, 1902.
18. Nothnagel: Specielle Pathologie u. Therapie **7**:175, 1913.
19. Wells: Chemical Pathology, Ed. 4, Philadelphia, W. B. Saunders Company, 1920.
20. Erben: Ztschr. f. klin. Med. **40**:266, 1900.
21. Rumpf: Berl. klin. Wchnschr. **38**:477, 1901.
22. Fowell: Quart. Jour. Med. **6**:179, 1913.
23. Kennerknecht: Virchow's Arch. f. Path. u. Physiol. **205**:89, 1911.

Hunter [24] and Finney,[25] but this was not confirmed by Queckenstedt.[26] He, however, used less accurate methods.

The fact that there is an excess of one of the basic products of hematopoiesis, iron, indicates that rapid hemolysis is an underlying factor. Experimentally the blood picture of this disease can be reproduced by poisoning with toluylendiamin,[27] the toxin of *Bothriocephalus*,[28] *p*-oxyphenylethylamin,[29] *Trypanosuma equiperdum* [30] and *Oestrus equi* larvae in horses.[28] The causative agent of pernicious anemia has never been identified. It has been suggested that the disease was due to a toxin arising from unknown infection, from intestinal putrefaction, from faulty metabolism or from atrophy of the hematogenic organs.[31]

Not only is there an increase in the free or inorganic iron in the blood, but much is stored in the tissues, particularly in the liver and kidneys. Hunter [24] in a series of seven cases of pernicious anemia and seven control cases found that the iron content of these organs was as follows:

	Average Per Cent. of Iron		
	Liver	Kidneys	Spleen
Pernicious anemia (7)	0.270	0.090	0.125
Control (7)	0.075	0.011	0.355

The relative increase is most marked in the kidneys. Ruffel [32] has obtained similar, but less striking results. Squier [33] gives the following analytic figures for normal and hemolytic anemic guinea-pigs:

	Liver	Kidneys	Spleen
Normal pigs	4.62	0.54	0.24
Anemic pigs (hemolysis)	25.02	3.69	2.49

These data further support the contention that there is an iron retention in hemolytic anemia. Muir and Dunn [34] working with hemolysis in rabbits found an increase in the iron content of almost five times the normal in the liver and kidneys, but no uniform increase in the walls of the stomach or intestines. Their findings are confirmed

24. Hunter: Lancet **1**:283, 1903.
25. Finney: Brit. M. J., 1880.
26. Queckenstedt: Ztschr. klin. Med. **79**:49, 1913.
27. Syllaba: Abst. in Folia Hematol. **1**:283 and 289, 1904.
28. Seyderhelm: Arch. exper. Path. u. Pharm. **76**:149, 1914.
29. Iwao: Biochem. Ztschr. **59**:436, 1914.
30. Krumbhaar: Jour. Infect. Dis. **22**:34, 1918; Steinfield: Plasma Chlorids in Anemia, Arch. Int. Med. **23**:511 (April) 1919.
31. Bunting: Bull. Johns Hopkins Hosp. **16**:222, 1905.
32. Ruffel: J. Path. & Bacteriol. **14**:411, 1910.
33. Squier: J. Lab. & Clin. Med. **2**:552, 1917.
34. Muir and Dunn: J. Path. & Bacteriol. **19**:417, 1914.

by Boycott and Jones.[35] Muir and Dunn[36] found later that if the animals were permitted to recuperate and the blood hemoglobin returned to the normal, there was no longer any evidence of iron retention in the tissues; they concluded that the iron is utilized by the bone marrow. Thus it is clear that in hemolytic anemias, as in pernicious anemia, there is a marked renal deposition of iron.

The exact location and distribution of this retained iron or siderosis is interesting. It occurs in other disorders than pernicious anemia, especially in bronze diabetes and hemochromatosis. The deposition of iron in the kidney is practically constant in its distribution. It exists as a granular deposit in the cells of the convoluted tubules, both proximal and distal. In some instances of excessive deposition it is also found in the cells of the thick limb of Henle's loop. The iron derivative of hemoglobin[37] has been thought of by Quincke[38] and Hunter[39] as an iron albuminate with the iron in loose combination. Gaskell and his co-workers[40] reported the siderosis confined to the convoluted tubules in the kidney in bronze diabetes. Sprunt[41] found iron containing pigment in the secreting cells of all glands examined in three cases of hemochromatosis, and in the kidneys it was confined to the convoluted tubules and the lumina of the collecting tubules. Corresponding to our later experimental findings,[1] he states that some of the tubule cells are heavily laden with iron, while immediately adjacent tubules are entirely free from it. Stühlen[42] reports similar findings. Muir and Dunn[34] in their experimentally produced hemolytic anemias in rabbits found granules of hemosiderin in the cells of the convoluted tubules and a marked iron reaction there, but nowhere else in the renal tissue. Muir and M'Nee,[43] in studying hemoglobinuria found iron retained in the convoluted tubule cells, occurring twenty-four hours or less after hemolysis. They postulate that this may occur after hemolytic intoxication even without hemoglobinuria. In studying the increased urinary output of iron in pernicious anemia, Rous[44] found desquamated cells containing hemosiderin in fresh urine. Among his ten cases, eight showed this positive indication of renal hemosiderosis. He advocates search for such cells as a diagnostic measure.

35. Boycott and Jones: Jour. Path. & Bacteriol. **16**:347, 1913.
36. Muir and Dunn: J. Path. & Bacteriol. **20**:41, 1916.
37. Strasser: Ziegler's Beitr. z. path. Anat. u. all. Path. **70**:248, 1922.
38. Quincke: Deutsch. Arch. f. klin. Med. **25**:580, 1880; **27**:193, 1881.
39. Hunter: Lancet, November and December, 1892.
40. Gaskell, Sladden, Wallis, Vaile and Garrod: Quart. J. Med. **7**:129, 1914.
41. Sprunt, T. P.: Hemochromatosis, Arch. Int. Med. **8**:75 (July) 1911.
42. Stühlen: Deutsch. Arch. f. klin. Med. **54**:248, 1895.
43. Muir and M'Nee: J. Path. & Bacteriol. **16**:410, 1911.
44. Rous: J. Exper. Med. **28**:645, 1918.

Rous and Oliver,[45] in a histologic study of renal siderosis in rabbits, found iron only in the distal convoluted tubules and in the ascending limb of Henle's loop. These observers, as well as all the workers mentioned in the foregoing, report that there is no iron to be demonstrated in the glomerular space or in Bowman's capsule. Dubin and Pearce [46] report that in severe hemolytic anemias there is no increased iron output in the urine and feces, but their work had to do with fecal rather than urinary elimination. Warthin [47] also reports eight cases of pernicious anemia, all showing renal hemosiderosis with the iron confined to the convoluted tubules.

Experimental production of renal hemosiderosis has shown [1] the same histologic distribution. The iron is usually confined to the cells of the convoluted tubules, but in some instances appears also in the cells of Henle's loops. It may be concentrated in some cells, whereas neighboring tubules may contain little or none of it. Schurig [47] found similar marked renal siderosis following daily injection of horse hemoglobin. McMaster, Rous and Larimore [48] using hemoglobin as prepared by the method of Sellards and Minot,[49] found that the renal siderosis affected primarily the proximal convoluted tubules and the ascending limb of Henle's loop, just as in pernicious anemia. But they believe that the Cushny [50] reabsorption theory of urinary secretion holds good for iron and that this iron is reabsorbed from the tubule lumen. This theory has been proved incorrect for iron.[1] In studying the renal elimination of bilirubin, Haesler, Rous and Brown [51] found that the pigment accumulates, as does hemosiderin, in the convoluted tubules and Henle's loop, but the glomeruli are unstained. This is confirmed by Quincke's previous observations.[52] In coexistant renal disease, bilirubin may not come through, but be stored in the renal cells (Nonnenbruch [53]). Fukuda and Oliver,[54] in studying the excretion of hemoglobin by the kidney in animals, believed that at least some of the pigment was secreted by the cells of the convoluted tubules, and that all of it did not pass through, but was retained.

The uniformity of these pathologic and experimental reports is striking. The convoluted tubule cells are almost universally conceded as being the site of secretion and deposition of iron containing pigments, or simple iron salts. To the foregoing data can be added a

45. Rous and Oliver: J. Exper. Med. **28**:629, 1918.
46. Dubin and Pearce: J. Exper. Med. **25**:675, 1917; Ibid. **27**:479, 1918.
47. Schurig: Arch. Exper. Path. u. Pharm. **41**:29, 1898.
48. McMaster, Rous and Larimore: J. Exper. Med. **35**:521, 1922.
49. Sellards and Minot: J. M. Res. **37**:161, 1918.
50. Cushny: The Secretion of Urine, Monographs of Physiology, 1917.
51. Haesler, Rous and Brown: J. Exper. Med. **35**:533, 1922.
52. Quincke: Nothangel's Specielle Path. u. Therap. **18**:83, 1899.
53. Nonnenbruch: Mitt. Grenzgeb. Med. u. Chir. **21**:470, 1919.
54. Fukuda and Oliver: J. Exper. Med. **37**:83, 1923.

report of fifteen * cases of pernicious anemia in which the kidneys were studied by the direct Prussian blue reaction for iron,[1] rather than by the method of Nishemura,[55] which is more complex and no more satisfactory.

In fourteen of the fifteen cases, a deposition of iron in the cells of the convoluted tubules was demonstrable. Of these cases, seven, or about one-half, showed only a small amount; the other, a great deal. The iron reaction was always sharply localized, never diffuse, and showed iron present only in the cell membrane of the convoluted tubules or in the débris in the lumina. No iron was detected in the glomerular spaces or capsule. The cases showing the largest amount of iron in the tubules had a lower hemoglobin reading at the time of death than the others. The average hemoglobin content of the blood in three cases with only a little iron retained was 45 per cent.; the average hemoglobin for five cases with marked deposition of iron was 17 per cent.

Having established that in pernicious anemia there is a marked deposition of iron in the cells of the convoluted tubules, the next problem is: What effect has this iron on renal function? The fact that the renal disorder is usually worse when the anemia is most marked may be explained in two ways: either the anemia is the direct cause of the renal disturbance, or at that time the renal siderosis is most marked and therefore the effect of the iron most conspicuous.

Sellards and Minot [56] found that considerably less hemoglobin is required for injection to produce hemoglobinuria in persons with pernicious anemia than in normal persons. In secondary anemia or in any case in which there is no excessive destruction of blood the renal threshold for hemoglobin is about normal. They found, further, that the hemoglobin tolerance bore no relationship to the red corpuscle count, but varied inversely with the amount of blood destruction taking place at the time. This finding is interesting in connection with the deposition of iron (which also depends on the amount of blood destruction going on), for the cells are already loaded with iron compounds and therefore cannot retain the excess as would normal cells, which are practically free of ionizable iron. The lowered threshold therefore may be largely explained by the renal siderosis.

It was thought that an experimental study of the renal function in anemias with and without renal hemosiderosis and in hemosiderosis

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* The material from these fifteen cases was collected through the courtesy of Dr. E. B. Krumbhaar, Philadelphia General Hospital; Dr. H. Oberhelman, Presbyterian Hospital, Chicago; Dr. H. G. Wells, University of Chicago, and Dr. L. Stieglitz, New York. I take this opportunity of expressing my appreciation of their kind cooperation.

55. Nishemura: Centralbl. f. allg. Path. u. Path. Anat. **21**:10, 1910.

56. Sellards and Minot: J. M. Res. **34**:469, 1916.

without anemia might throw further light on the point of view that the iron deposition in the kidney is largely responsible for the renal damage in pernicious anemia. The tabulated protocols of such experiments follow.[57]

PROTOCOLS OF EXPERIMENTS

EXPER. 1.—*Simple Secondary Anemia.*—Dog, male, weight, 15 kilograms.

Nov. 15, 1922: Healthy dog; hemoglobin, 95 per cent. (Dare).[57] Urine: No albumin or casts, acid, specific gravity 1.032. Intravenous "phthalein": excreted 90 per cent., overnight.[57]

Nov. 16, 1922: Bled 300 c.c.; hemoglobin after bleeding, 80 per cent.

Nov. 20, 1922: Bled 300 c.c.; hemoglobin after bleeding, 70 per cent.

Nov. 23, 1922: Bled 200 c.c.; hemoglobin after bleeding, 65 per cent.

Nov. 26, 1922: Bled 200 c.c.; hemoglobin after bleeding, 50 per cent. Urine: No albumin or casts, acid, specific gravity 1.030.

Dec. 3, 1922: Bled 300 c.c.; hemoglobin after bleeding, 40 per cent.

Dec. 6, 1922: Bled 200 c.c.; hemoglobin after bleeding, 35 per cent.

Dec. 10, 1922: Bled 150 c.c.; hemoglobin after bleeding, 30 per cent. Later in day: hemoglobin, 35 per cent. "Phthalein," overnight, 82 per cent. Urine: No albumin or casts.

Dec. 15, 1922: Hemoglobin, 40 per cent. "Phthalein" overnight, 86 per cent. Urine: No casts or albumin.

EXPER. 2.—*Simple secondary anemia.*—Dog, male, weight, 10 kilograms.

Nov. 17, 1922: Hemoglobin, 93 per cent. "Phthalein" overnight, 88 per cent. Urine: No albumin or casts, acid, specific gravity 1.029.

Nov. 18, 1922: Bled 300 c.c.; hemoglobin after bleeding, 85 per cent.

Nov. 20, 1922: Bled 200 c.c.; hemoglobin after bleeding, 78 per cent.

Nov. 23, 1922: Bled 150 c.c.; hemoglobin after bleeding, 72 per cent.

Nov. 26, 1922: Bled 200 c.c.; hemoglobin after bleeding, 65 per cent. Urine: no albumin or casts.

Nov. 28, 1922: Bled 200 c.c.; hemoglobin after bleeding, 55 per cent.

Nov. 29, 1922: Bled 150 c.c.; hemoglobin after bleeding, 50 per cent. Urine: no albumin or casts, clear, acid, specific gravity 1.024.

Dec. 4, 1922: Bled 150 c.c.; hemoglobin after bleeding, 47 per cent.

Dec. 8, 1922: Bled 200 c.c.; hemoglobin after bleeding, 40 per cent. Urine: no albumin or casts, clear acid. "Phthalein," overnight, 80 per cent.

Dec. 12, 1922: Bled 200 c.c.; hemoglobin after bleeding, 32 per cent. Urine: still perfectly normal.

The animal was not killed, but allowed to recover and used later for other work.

The results of these two experiments indicate that simple secondary anemia alone does not cause any conspicuous change in renal function or kidney damage as manifested by albumin and casts.

EXPER. 3.—*Secondary Anemia with Reinjection of Hemoglobin.*—Dog, female, weight, 12 kilograms.

Dec. 10, 1922: Hemoglobin, 92 per cent.; "phthalein" overnight, 90 per cent. Urine: no albumin or casts, clear, acid, specific gravity 1.028. Bled 300 c.c.;

57. The Dare instrument was used throughout for hemoglobin estimations. The phenolsulphonephthalein test was carried out by injecting 1 c.c. of the ampule solution of the dye intravenously in the evening and collecting all the urine the next morning from the metabolism cage. This was then titrated against a standard in the usual way.

hemoglobin after bleeding, 80 per cent. The blood centrifuged, corpuscles separated, washed and then hemolyzed with distilled water; 50 c.c. of this were reinjected intravenously.

Dec. 11, 1922: Hemoglobinuria.

Dec. 13, 1922: Bled 200 c.c.; hemoglobin after bleeding, 78 per cent. Corpuscles treated as above, and 40 c.c. of hemoglobin solution injected intravenously. Hemoglobinuria followed promptly.

Dec. 14, 1922: Hemoglobinuria; no casts or albumin detected.

Dec. 15, 1922: Urine clear, no casts or albumin.

Dec. 16, 1922: Bled 400 c.c.; hemoglobin after bleeding, 60 per cent. 400 c.c. of hemoglobin solution reinjected as above.

Dec. 18, 1922: Bled 300 c.c.; hemoglobin after bleeding, 51 per cent; 35 c.c. of hemoglobin solution reinjected as above. Hemoglobinuria.

Dec. 20, 1922: Bled 250 c.c.; hemoglobin after bleeding, 40 per cent. Hemoglobin solution reinjected as above.

Dec. 21, 1922: Urine: Clear, both albumin and casts present and a trace of hemoglobin; specific gravity, 1.018.

Dec. 22, 1922: Urine: Clear, albumin and casts both present, no hemoglobin; specific gravity, 1.016, acid. Bled 300 c.c.; hemoglobin after bleeding, 28 per cent.

Jan. 10, 1923: Urine: Clear, dark straw, albumin and casts both present; acid; specific gravity, 1.024. Bled 300 c.c.; hemoglobin after bleeding, 34 per cent. Hemoglobin reinjected as above. Hemoglobinuria occurred as before, but there was less in the urine than previously.

Jan. 13, 1923: "Phthalein" overnight, 60 per cent.

Jan. 15, 1923: Hemoglobin, 40 per cent. Urine: Albumin and casts both present, especially the former. No hemoglobinuria; specific gravity, 1.014.

The above experiment, on the other hand, indicates that an anemia with hemoglobinemia and therefore renal hemosiderosis leads to distinct renal damage as evidenced by the fall in the phenolsulphonephthalein excretion from 90 to 60 per cent. and the appearance of albuminuria and casts.

EXPER. 4.—*Experimental Hemosiderosis Without Anemia.*—Dog, terrier, female, weight, 7,680 gm.

Jan. 12, 1923: "Phthalein" overnight, 90 per cent. Urine: Clear, dark amber, no albumin or casts, or sugar. Specific gravity, 1.05.

Jan. 13, 1923: Injection of 1 gm. of green ferric ammonium citrate partly intravenously, partly subcutaneously; marked amount of iron in urine after the injection.

Jan. 16, 1923: Injection of 0.75 gm. green ferric ammonium citrate intravenously. Afterward there was a great deal of iron in the urine. "Phthalein" overnight, 65 per cent. Urine: A few hyaline casts (some with iron in them), and some albumin; specific gravity, 1.02, acid.

This experiment unfortunately was discontinued because of an illness of the author.

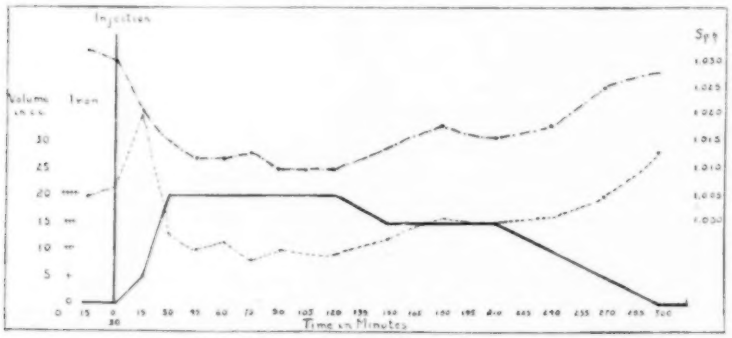
It has been shown in rabbits[1] that iron is secreted by the convoluted tubules, and that in the process of this secretion it causes distinct functional changes. The foregoing experiment partly confirms this finding in a dog. During the period of elimination of iron following intravenous injection of iron salts, there is a brief and transient

diuresis, followed by an antidiuresis. Furthermore, in rabbits, during iron elimination by the kidneys the specific gravity of the urine is lowered, and thus not only the volume of the urine, but the total solids are reduced by the action of the iron.

The following experiment shows that the same results may be obtained in a dog.

EXPER. 5.—Dog, female, weight, 8 kilograms. The animal was tied to the table, catheterized without anesthesia, and the urine collected, the catheter being left in place and new specimens obtained every fifteen minutes. After two preliminary control readings, 0.8 gm. of green ferric ammonium citrate were injected into the jugular vein with no apparent toxic reaction. The results are shown graphically in the chart.

The foregoing experiment reproduces the results previously obtained with rabbits and shows that iron has a decided effect on renal function



Results in Experiment 5. The continuous line indicates the iron in the urine; the broken line, volume of urine per unit of 15 minutes in cubic centimeters; dot and dash line, specific gravity of urine.

during the time of its elimination. Iron, during its elimination by the kidneys, causes a fall in the rate of water excretion and a fall in the specific gravity, indicating a marked diminution of all secretion at that time.

COMMENT

That iron is retained in the convoluted tubule cells in pernicious anemia has been demonstrated. It has also been shown that there is an increased secretion of iron salts in the urine. Iron retained in the tubular epithelium in rabbits may gradually cause a mild nephritis, or disturbance of renal function, as indicated by the appearance of albuminuria and casts, and in some instances ascites. Trivalent iron, according to Fischer,[58] is the most active of all cations in preventing

58. Fischer: Edema and Nephritis, New York, John Wiley & Sons, 1915.

the hydration of colloids, or in freeing water from them. It should therefore be an active diuretic. It is diuretic in the initial phases of the experiment, while there are free iron ions in the tissues and circulation, but as soon as it accumulates in the secreting cells the reaction would be reversed, as is the case. The presence of iron in the cells in abnormal quantity prevents their taking up water and therefore the resulting antidiuresis. The fall in the specific gravity of the urine is likewise dependent on this phenomenon, as the solutes cannot pass if their solvent, water, is blocked. This all points to a secretory function for the convoluted tubules, which in pernicious anemia is interfered with by the accumulation of iron in the cells of the convoluted tubules.

The effect of iron on the urine volume and specific gravity is particularly interesting in view of the clinical observation on renal function in pernicious anemia, in which the ability of the kidney to concentrate the urine is most characteristically affected. The relation between these two phenomena, clinical and experimental, seems more than coincidental, and it may be concluded that this correlation of findings is of significance in connection with the etiology of the nephritis, or renal damage of pernicious anemia.

The intracellular activities of iron are not all injurious, however. Bayliss [59] emphasized the important function of iron compounds as vehicles for oxygen, to be consumed elsewhere. This is also pointed out by Peters.[60] However, the iron so utilized is not electrolytic, inorganic iron. Ferric compounds do not carry oxygen, but are catalytic in stimulating the tissues to consume oxygen.[61] Thurnburg [62] observed that lecethin consumed oxygen in the presence of iron salts, but not without them. Therefore ionized iron has a powerful chemical catalytic action in stimulating oxidation as well as the physical action discussed in connection with colloid hydration and diuresis.

The therapeutic use of iron in pernicious anemia is a common method of treatment, used formerly more than it is now. Recent work has shown that iron is of little value in the treatment of this disease. This conforms with the knowledge that there is a superabundance of this element already in the tissues. Musser [63] showed that inorganic iron did not increase the speed of blood regeneration in dogs rendered

59. Bayliss: Principles of General Physiology, New York, Longmans, Green & Co., 1915, (pp. 592 and 614).
60. Peters: Jour. Physiol. **44**:131, 1912.
61. Warburg: Ergeb. Physiol. **14**:253, 1914.
62. Thurnburg: Skand. Arch. Physiol. **24**:90, 1911.
63. Musser: Influence of Inorganic Iron on Regeneration of Blood After Hemorrhagic Anemia, Arch. Int. Med. **28**:638 (Nov.) 1921.

secondarily anemic. Whipple and Robscheit [64] obtained similar results, and Whipple [65] found that arsenic and iron were inert in this connection. Weber [66] and Ashby [67] come to the same conclusion, the latter even questioning whether there is an increased hemolysis. Whipple [64] concludes that the deficiency is in the stroma material necessary for the manufacture of erythroplastids rather than in the hemoglobin factor.

SUMMARY

It has been shown that:

1. Disturbances of renal function are common in pernicious anemia.

2. Histologic examination of the kidneys frequently discloses degeneration of the tubular epithelium.

3. There is a deposition of iron in the convoluted tubules of the kidney.

4. Iron in such a location probably causes damage to the epithelium.

5. Iron in these cells inhibits the passage of water and total solids, and reduces the specific gravity of the urine.

6. Fixation of the specific gravity and an increase of the night over the day urine volume is characteristic of the alteration of renal function in pernicious anemia.

The correlation of these findings leads to the conclusion that the renal functional changes in pernicious anemia may be attributed at least in part to the accumulation of iron in the convoluted tubules, rather than to the anemia alone. The hemosiderosis and the resulting changes in function are so specific that one may speak of this condition as the nephritis of pernicious anemia. It is particularly interesting in view of the fact that the changes are apparently purely tubular and result from a perverted metabolism.

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64. Whipple and Robscheit: Iron and Arsenic as Influencing Blood Regeneration Following Simple Anemia, Arch. Int. Med. **27**:291 (May) 1921.

65. Whipple: Pigment Metabolism and Regeneration of Hemoglobin in the Body, Arch. Int. Med. **29**:711 (June) 1922.

66. Weber: Ztschr. f. Biol. **70**:168, 1920.

67. Ashby: J. Exper. Med. **34**:127, 1921.

PARALYSIS OF THE LEFT RECURRENT LARYNGEAL NERVE IN MITRAL STENOSIS

REPORT OF A CASE, AND A REVIEW OF THE LITERATURE *

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During the past twenty-five years a rather uncommon complication of mitral stenosis, paralysis of the left recurrent laryngeal nerve, has caused considerable interest. The chief importance of the condition lies, perhaps, in the diagnosis, more especially in its distinction from aortic aneurysm; but in addition there has been a great deal of controversy and discussion as to the method of production of the paralysis and its course and termination. Since Ortner first described the condition (1897), four different theories and many modifications have been proposed as to its mechanism, and each has for its support not only the opinion of various clinical investigators, but also the findings in a number of necropsies. Seventy-four cases have been reported, in seventeen of which necropsy was performed.

It is my purpose to report a case diagnosed, treated and examined postmortem in the Montreal General Hospital; to review the literature; to discuss the diagnosis, the method of production of the paralysis, the treatment and prognosis.

REPORT OF A CASE

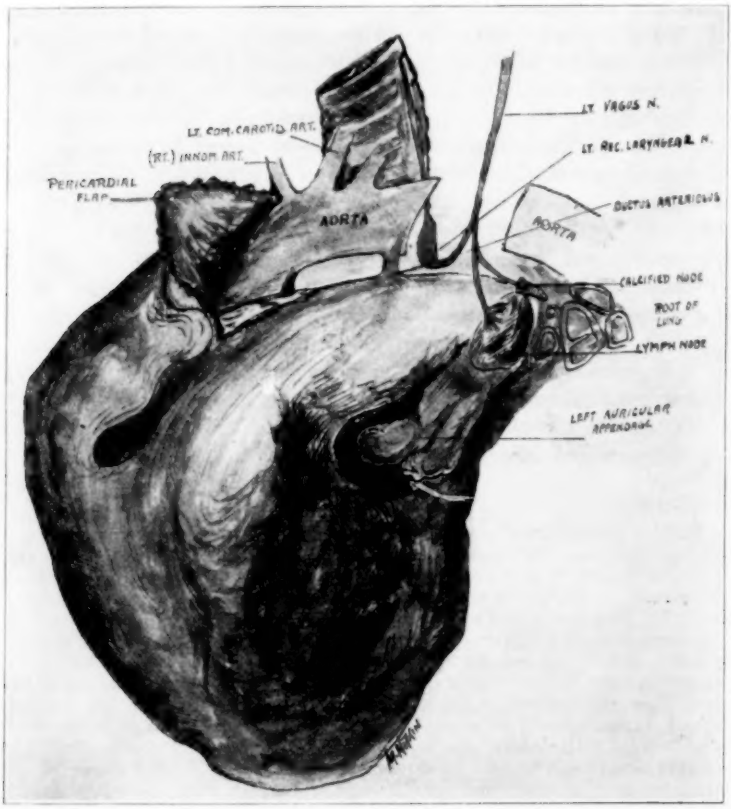
M. G. H., a man, aged 31, in the service of Dr. F. G. Finley, complained of dyspnea, weakness and swelling of the legs and abdomen. For the past three and a half years he had been troubled with dyspnea, palpitation of the heart and edema, on account of which he had to stop work for several months at a time. On March 1, 1921, he was admitted to the Montreal General Hospital and was discharged in one month, improved. Three weeks later he was readmitted with the same symptoms. He assumed the orthopneic position. A systolic impulse in the veins extended up each side of the neck as far as the ears. There was edema of the lower extremities and scrotum. The abdomen showed dilated superficial veins. The liver was slightly enlarged. The fundi were normal. The pulse was irregular in volume and rhythm. The blood pressure was: systolic, 118; diastolic, 82. There was some bulging of the precordium. The apex beat was diffuse in the left fifth and sixth spaces. The maximum impulse was 11 cm. to the left of the midsternal line. The upper limit of dulness was at the second costal cartilage and the right border 5 cm. from the midsternal line. At the apex there was a blowing systolic murmur propagated toward the axilla and along the sternum. The second sound was followed by a faint murmur. At the base the second pulmonary sound was accentuated. (Dr. F. G. Finley.)

Roentgen-Ray Report (Dr. Wilkins).—Roentgen-ray examination of the chest showed marked increase in the transverse diameter of the heart at the apex,

* From the service of Dr. F. G. Finley and the pathological laboratories of the Montreal General Hospital.

both to the right and to the left. No abnormality was noted as being associated with the aortic shadow, and the upper portion of the posterior mediastinum was clear.

Course of Disease.—The abdomen was tapped every two or three weeks, and between 6,000 and 8,000 c.c. of turbid, straw-colored fluid were withdrawn each time. Infarcts of the lung developed. Six days before death hoarseness appeared and remained until death. A laryngoscopic examination by Dr. R. P. Wright revealed: almost complete limitation of movement of the left cord;



Semidiagrammatic drawing of heart as found in author's case. Aorta, pulmonary artery and lymph node are shown to be drawn apart. A section of the aorta is shown to be removed, exposing the left vagus nerve as it hooks around the aorta.

marked thickening and some interarytenoidal bogginess. The right cord moved freely and was greatly thickened and slightly reddened.

Anatomic Findings.—The body was well developed but emaciated. The conjunctivae were jaundiced. The skin was dry and scaly; the abdomen distended and the superficial veins dilated. There was chronic passive congestion

of the lungs, liver, spleen, kidneys and mesenteric veins. There were multiple infarcts of the lung; fibrous pleural adhesions on the left side; cirrhosis of the liver (slight), ascites, edema (slight) and jaundice.

The heart was large, the myocardium firm and brownish. The left auricle, right auricle and right venntricle were all markedly dilated and hypertrophied, while the walls of the left ventricle were not noticeably thickened.

The cusps of the mitral valve were fused and calcified, leaving an orifice measuring 1.7 cm. by 0.8 cm. The tricuspid valve was normal except for the anterior cusp, which was slightly thickened at the free edge. The left anterior and the posterior cusps of the aortic valve were considerably thickened about the nodule of each cusp. The pulmonary valve was free.

The pulmonary artery was considerably dilated (3.75 cm. at its widest diameter), and in the angle between the pulmonary artery, aorta and ductus arteriosus (nonpatent) was lodged a lymph gland (1.5 cm. by 1.25 cm.), lending itself in this position as additional means of transmitting pressure upon the aorta and directly upon the recurrent laryngeal nerve.

The left recurrent laryngeal nerve as it hooked under the aorta showed marked flattening and was pale gray. The remainder of the left vagus divided into two main branches: One branch ran through the connective tissue at the base of the lymph gland mentioned above (to form the anterior pulmonary plexus), and another ran toward the posterior aspect of the root of the lung. On its course this branch was held fast in a calcified lymph node lying a little in front of and below the aorta. It was difficult to determine whether or not during life this calcified mass exerted pressure upon the aorta and indirectly upon the left recurrent laryngeal nerve.

The trachea was somewhat flattened on the left side, at that area which is in contact with the arch of the aorta.

REVIEW OF THE LITERATURE

Theories of the Production of the Paralysis of the Vocal Cord.—1. Ortner, whose two cases came to necropsy, believed that the enlarged left auricle pressed the left recurrent laryngeal nerve against the aorta producing a pressure paralysis.

2. Kraus, in 1900, reported a case which at necropsy showed, besides a dilated left auricle, a greatly hypertrophied right ventricle which had forced the heart into a transverse position. He believed that the enlarged right ventricle had rotated on the diaphragm in such a way as to shift the base of the heart to a lower position, dragging with it the ductus arteriosus, which in turn pulled on the aorta with resultant traction on the left recurrent laryngeal nerve.

3. Von Schroetter described a case in which the mechanism was altogether different. There was a patent ductus arteriosus as large as the greatly dilated pulmonary artery, which pressed the laryngeal nerve against the aorta at the point of origin of the ductus.

4. Alexander's case, in 1904, without necropsy, showed on roentgenographic examination a dilated left auricle and pulmonary artery. In view of the normal anatomic relations of the left auricle, pulmonary artery, laryngeal nerve and aorta, he suggested that the paralysis was due to pressure of the pulmonary artery upon the nerve. Such a condition was actually found at necropsy by Frischauer (1905).

5. Other reports followed with discussions and additions, including the statement that the laryngeal nerve may be involved in the cicatricial tissue following pericarditis, mediastinitis and other lesions that may be associated with mitral stenosis.

COMMENT

Ortner's theory was supported by necropsy findings by Herrick, Hofbauer (Case 2), Ceraulo, Osler (Cases 1 and 3), Guder and Dufour (Case 2) and Bonardi, as well as the opinions of Sheldon, Thorne, Harris, Boinet, Palasse, Gouget, Perotta, Cohn and Sforza, based on observations on cases in which postmortem examinations had not been made. Some of them accepted Ortner's theory in cases in which there was cardiac decompensation and that of Kraus in cases in which compensation had produced an hypertrophied right ventricle.

Kraus, Dmitrenko and others take exception to Ortner's view on the ground that the left ventricle is separated from the left recurrent laryngeal nerve by the pulmonary artery, and therefore cannot itself press upon it. They point out that there are many cases of extreme dilatation of the left auricle from other causes than mitral stenosis, but in such cases paralysis of the left recurrent laryngeal nerve is unknown.

Fetterolf and Norris by cross sections and dissections of formaldehyd hardened thoraces have shown the position of the left auricle to be such that

> In expansion, the auricular appendix would probably be the first part affected as it lies free and unadherent to anything. Should it be dilated it would press upward and backward, thrusting the left pulmonary artery against the aorta, the left pulmonary vein against the pulmonary artery and forcing the distal portion of the latter against the aorta. Later when the atrium or main cavity dilated the proximal part of the pulmonary artery is jammed upward and backward, mainly by the root of the left pulmonary vein. The nerve is thus squeezed between the pulmonary artery on the one hand and the aortic arch or ligamentum arteriosum on the other.

This report, antagonistic to Ortner's and Kraus' theories, strengthens the view of Alexander and Frischauer, which has for its support the necropsy reports of Frischauer, Mead, Garland and White and our own case, and the views of Dmitrenko, Lian and Marcolles, Carrau, Guttman and Neuhoff and also Gillies, who described in a case without mitral stenosis a paralysis of the recurrent nerve due to pressure of a dilated pulmonary artery.

Lian and Marcolles claim that additional etiologic factors are necessary. They suggest that there should be something of sufficient hardness to compress the nerve, and propose either the presence of old thrombotic masses in the left auricle or a certain degree of chronic mediastinitis.

Kraus, who had the support of Hofbauer, Quadrone and others, states that at necropsy in his case the ductus arteriosus was found to lie in a horizontal position and therefore must have been pulled down by the rotated heart. Fetterholf and Norris have shown that this horizontal position of the ductus is the normal one, and state that even if in Kraus' case its position was more nearly horizontal than usual it was probably caused by a pushing up of the pulmonary artery. Moreover, it is hardly likely that the ductus, a structure of about 2 mm. in diameter, would produce the descent of a large structure like the aorta, supported and held in position as it is by the great vessels which arise from it, as well as the deep cervical fascia and other structures.

Von Schroetter's findings of incarceration of the nerve by the patent ductus and aorta have also been reported by Zimbler and Mead. Gerhardt affirmed the possibility of paralysis of the recurrent nerve due to this cause.

It appears, therefore, that if any one mechanism is adopted to explain the production of the paralysis, preference must be given to that in which the pressure of the pulmonary artery upon the nerve (whether due to enlargement of the artery or to its displacement) is the major factor. Here it is not necessary to strain the imagination since the anatomic position of the parts is such that on enlargement of the heart the pulmonary artery must come in contact with the nerve. Moreover, hypertrophy and dilatation of the pulmonary artery occurs in most of the reported cases.

PARALYSIS OF THE LEFT RECURRENT LARYNGEAL NERVE

Paralysis of this nerve produces a change in the character of the voice varying from a low pitch to aphonia, depending on the extent to which the nerve is affected. The onset may vary both in the stage of the cardiac disease at which it occurs and in the rapidity of onset.

Stage of Disease at Which Paralysis Occurs.—The reported cases may be divided into four groups: (1) those in which paralysis occurs while compensation is still good—eight cases; (2) those in which compensation is fair as evidenced by dyspnea, etc., but no edema—seventeen cases; (3) cases in which compensation is broken—twenty-three cases; (4) cases in the agonal stage in which paralysis occurs a few days before death—four cases. Most cases occur when there is a disturbance of compensation with consequent dilatation of the heart. Sometimes, however, as in the cases of Hofbauer (Case 1), Thorne, Alexander, Davis, and Hall, the patient primarily comes to seek the advice of the laryngologist for hoarseness, and the cardiac condition is found in the subsequent examination.

Analysis of the Reported Cases

Reporter	Patient		Heart Lesion	Brief History	Pulses	Pulsation at 2d Cartilage	Recurrent Paralysis	Change of Voice on Position	Roentgen Ray	Necropsy	Remarks
	Age	Sex									
Ortner.....	17	M	Double mitral and tricuspid stenosis obliterating pericarditis	Venous pulse in neck; dyspnea and orthopnea; edema, ascites	Left carotid smaller than right	.....	0	.....	.....	Auricle compressed nerve against left bronchus; pericarditis; pulmonary artery dilated	Nerve degenerated; auricle filled with coagulated blood; thrombus right pulmonary artery
	34	F	Double mitral and aortic, tricuspid stenosis, adherent pericarditis	Rheumatic arthritis for 12 years; last 2 years short breath, weak on exertion; lately edema and hoarseness; large liver; anasarca	.....	.....	Reappears from time to time	.....	.....	Nerve compressed between left auricle and aorta	Nerve flat and discolored; right vein dilated
Herrick.....	38	M	Mitral stenosis, obliterative pericarditis and pleuritis	Two years ago chest pain and edema; hoarseness ½ year ago (6 months after patient had pleurisy and pericarditis)	.....	.....	.....	.....	.....	Nerve embedded in cicatricial tissue and compressed between aorta and left auricle which forced its way between aorta and pulmonary artery, considerably distorting normal anatomic relations; nerve microscopically degenerated	Compression probably due to: (1) Cicatrical contraction; (2) auricular pressure
Kraus.....	21	F	Double mitral, tricuspid insufficiency, aortic stenosis (slight)	Heart disease since 4 years; no decompensation mentioned	Rapid, irregular	.....	.....	.....	Transverse position of heart	Right ventricle so large that heart is rotated pulling on pulmonary artery, aortic ligament and aorta and resulting in traction on nerve; nerve gray and degenerated	Right ventricle only forms apex; in spite of size of auricle it was 4 cm. away from point of strangulation
Von Schroetter	15	F	Double mitral, tricuspid insufficiency, patent ductus arteriosus	Effort syndrome since childhood; cyanosed since birth; congestion of abdominal organs; edema	.....	1st and 2d	.....	.....	At upper left border there is curve at 2d cartilage which is not dull to percussion	Nerve compressed between origin of ductus arteriosus and aorta, constricted and discolored; pulmonary artery larger than ascending aorta, its branches larger than normal; ductus arteriosus as large as pulmonary artery	Pulmonary artery dilated; nerve discolored; on phonation tremulous movement of left arytenoid cartilage
Hofbauer....	32	M	Mitral stenosis	Feeling of oppression for 2 months; short of breath; soon after this hoarseness which made him seek medical aid	.....	.....	.....	Worse in left lateral decubitus or on bending forward	Two pulsating shadows at left border of heart due to left auricle and pulmonary artery	None	
Syllaba.....	47	M	Mitral stenosis	.....	.....	.....	.....	.....	.....	None	
Sheldon.....	38	F	Mitral stenosis	Heart disease 2 years ago, 1 year later dyspnea, edema, etc.; improved; 6 months later recurrence sudden, and next morning could talk only in whisper; 1 week later heart-improved, voice normal	.....	.....	Improved with heart condition	.....	.....	None.....	Both cords worked normally on discharge

Quadrone	1	..	F	Mitral stenosis and insufficiency	Bilateral paresis						Nerve histologically normal
	2	.	F	Mitral stenosis	Bilateral paresis						None
	3	..	F	Double mitral lesion	Bilateral paresis						
	4	..	F	Double mitral lesion	Bilateral paresis						
	5	..	M	Double mitral lesion	Bilateral paresis						
	6	..	F	Mitral stenosis	Bilateral paresis						
	7	15	F	Mitral stenosis	Bilateral paresis						
	8	..	F	Double mitral lesion	Left recurrent paralysis						
Harris		28	M	Mitral stenosis	At 24, dyspneic; at 27, became worse and lost voice; venous pulse present in neck	Small, rapid				None	From aphonia patient improved greatly
Alexander		50	F	Mitral stenosis	Subject to cardiac attacks of rheumatic origin, last one 2 years ago, since then effort dyspnea; hoarse for 8 weeks only, but later recurred and remained, for which she sought medical advice; slight dyspnea; no cyanosis			Hoarse 8 weeks, normal 6 weeks		Same as Hofbauer	None
Frischauer		30	F	Double mitral, tricuspid insufficiency	Since 8 years, palpitation and pain in right side, last 2 weeks much worse; slight cyanosis; slight passive congestion; no edema	Equal, small				Same as Hofbauer	Nerve compressed between pulmonary artery and aorta by forward and upward pressure of left auricle and pulmonary vein	On phonation, cord moves imperfectly; ilg. botalli does not touch nerve
Cavello		19	F	Mitral stenosis	Fair compensation						None	Possibility of aortic disease
Hofbauer		30	M	Mitral stenosis	Heart disease since 2 years with hoarseness; skin livid; before this in good health						Nerve compressed between left auricular appendix and aorta, former being pushed upward between pulmonary artery and aorta	Symptoms of pericarditis appeared after onset of hoarseness
Pal		..	..								None	Brief verbal report
Trétrop		49	M	Mitral insufficiency				Paralysis appeared and disappeared as patient got worse or better			None	
Thorne		17	F	Mitral stenosis	Four years ago rheumatic arthritis, since then dyspnea; sought advice for hoarseness; patient did not appear to be suffering severely from heart disease	Equal				Enlargement to left; pulsatile curve on left side	None	Left pupil dilated
Bonardi		40	F	Double mitral tricuspid insufficiency, pericarditis							Nerve compressed between left auricle and pulmonary artery; auricle dilated	

Analysis of the Reported Cases—(Continued)

Reporter	Patient		Heart Lesion	Brief History	Pulses	Pulsation at 2d Cartilage	Recurrent Paralysis	Change of Voice on Position	Roentgen Ray	Necropsy	Remarks
	Age	Sex									
Gantz	30	M	Mitral stenosis and insufficiency	Cardiac disease for 4 months; 2 weeks before admission edema, and 2 weeks later complained of hoarseness; 3 weeks later complete aphonia; cardiac decompensation increased; died 4 days later					Dilatation of left auricle to left and upward; no aneurysm	Peribronchial and bronchial glands enlarged through venous engorgement and compressed the nerve; auricle dilated but at a distance from recurrent nerve	
Sforza	..	..					Voice ameliorated during period of compensation		Dilated and hypertrophied left auricle		
Ceraulo....1	..	..	Mitral stenosis		Small, rapid, irregular					None	No details
2	..	..	Mitral stenosis	Compensation fair	Small, unequal, irregular			No change		None	Paresis of left cord
3	..	..	Double mitral lesion	Compensation partial	Small, rapid, irregular			No change		None	Bilateral paresis of both cords; left more marked
4	..	..	Double mitral and relative insufficiency of tricuspid	Compensation good	Small, rapid, irregular					Dilated left auricle pressed on nerve against aorta	Right ventricle enlarged; an emotional occurrence increased symptoms, brought on hemiplegia (right) and increased hoarseness
Koelreutter	29	F	Mitral stenosis	Four years ago sudden attack of dyspnea while walking, brought home cyanosed, since then progressive hoarseness; 1 year ago improved under treatment; cyanosis; no edema	Small, irregular	2d, 3d, 4th			Shadow to left of chest meeting with heart shadow (not diagnosed)	None	Tracheoscope shows mediastinal tumor
Zimbler	26	F	Congenital pulmonary stenosis and insufficiency; patulous ductus arteriosum						As Von Schroetter	None	
Da Gradi et Fratti	25	F	Double mitral lesion	Cardiac disease of rheumatic origin for several years, last 2 years dyspnea on exertion, hoarseness, and when fatigued aphonia; slight edema of limbs	Small, irregular				Dilated left auricle	None	Under observation several months; paroxysms of dyspnea are more frequent and paralysis more complete
Guder and Dufour 1	43	F	Double mitral lesion	Cardiac disease of rheumatic origin; symptoms of decompensation and hoarseness					Enlarged heart	None	Partial paralysis

2	24	M	Double mitral lesion	Cardiac disease of rheumatic origin; voice changed a little while before onset of symptoms of decompensation	.....	.....	.....	.....	.....	Dilated auricle pressing on nerve	
3	42	F	Mitral stenosis, aortitis and aortic insufficiency	Heart disease well compensated; sudden aphonia and anginoid pains	.....	.....	.....	.....	Dilated heart; dilated aorta without sac	None	Aortitis and periaortitis probable cause of paralysis; no further report
Osler.....1	45	F	Mitral stenosis	Heart trouble since childhood, especially past year; 6 months ago change in voice, cyanosis, dyspnea, edema	.....	.....	.....	.....	Dilated auricle	None.....	No decompensation when paralysis occurred; patient improved with treatment; died 1 year later
2	27	F	Double mitral stenosis	Hoarse 1 year ago; two years later cardiac symptoms increased and hoarseness; after improving on treatment became completely paralyzed	Small, irregular	.....	Improved or grew worse with cardiac condition	.....	.....	None	
3	46	M	Double mitral aortic insufficiency	Heart disease 6 months, some edema and hoarseness; improved with treatment and recurred with decompensation	Irregular	2d, 3d, 4th, 5th spaces	As above	.....	Dilated auricle; no aneurysm	Nerve compressed between dilated auricle and aorta; right ventricle extremely dilated; nerve sclerosed, white and opaque	Clinical diagnosis, aneurysm
Palasse.....	20	F	Mitral stenosis and insufficiency	Cardiac disease for 3 years, since 1 year hoarseness, gradual onset and persistent cyanosis, edema, dyspnea	Regular small	.....	.....	.....	Greatly enlarged heart, especially left auricle; shadow triangular, few enlarged glands	None.....	Probable etiology is enlarged mediastinal glands; pericardial adhesions
Perotta	38	F	Mitral stenosis	.....	.....	.....	.....	.....	.....	None.....	Tertiary syphilis
Boinet.....1	25	F	Mitral stenosis, tricuspid lesion	Cardiac disease since typhoid 15 years ago; past few months had to stop work; became worse suddenly during dyspneic attack; decompensation	.....	.....	.....	.....	Dilatation of left auricle which author assumes presses on nerve	None.....	No improvement with digitalis; paralysis followed by death
2	23	F	Mitral stenosis		.....	.....	Several recurrences	.....	.....	None.....	+
Cohn.....	31	F	Double mitral lesion	Cardiac disease for 10 years, lately became more dyspneic on exertion and voice became deeper; no edema; positive venous pulse in the neck	Small, irregular, equal	3d and 4th	.....	.....	Dilatation of left auricle; root of aorta displaced to the right	None	
Dmitrenko...	29	M	Mitral stenosis	Since age of 7 cardiac disease of rheumatic origin; 2 years ago marked dyspnea and 2 months later hoarseness persisting to present (1 year)	Equal, rate 68; blood pressure, right 125, left 115	Pulsation at 2d cartilage easily seen	.....	.....	.....	None	
Mead.....	26	F	Mitral stenosis, aortic stenosis, patent ductus arteriosus, sclerosis of aorta	Congenital heart disease; subject to bronchitis; paralysis improved, then recurred with broken compensation	.....	.....	Recurred with heart decompensation	.....	.....	Dilated heart; left auricle and right ventricle extremely large; pulmonary artery dilated and larger than aorta; patent ductus arteriosus; nerve found microscopically to be not degenerated	

Analysis of the Reported Cases—(Continued)

Reporter	Patient		Heart Lesion	Brief History	Pulses	Pulsation at 2d Cartilage	Recurrent Paralysis	Change of Voice on Position	Roentgen Ray	Necropsy	Remarks
	Age	Sex									
Mosny and Portocolis	..	..	.....	.....	.....	.....	.....	.....	.....	....	Details not available
Fetterolf and Norris (Dr. F. H. Klaer)	29	M	Mitral stenosis and insufficiency	Onset of hoarseness without symptoms of heart trouble, sometimes relieved by belching; later with onset of cardiac symptoms, voice more hoarse with cough when in recumbent position; edema, dyspnea, dulness above heart and to the left of sternum	Left radial pulse smaller than right	.....	.....	.....	Heart enlarged to the left; bronchial lymph glands enlarged	None.....	Thoracic aneurysm diagnosed at first without roentgen ray examination; patient died
Vaquez and Bordet	..	..	.....	.....	.....	.....	.....	.....	....	....	Details not available
Claisse, 1 Thibaut and Gillard	22	F	Mitral stenosis	Onset of heart disease 2 years ago; 1 year ago voice changed and grew progressively worse; dyspnea, palpitation, cough	Regular, equal	.....	.....	No change	Dilated left auricle; no enlarged glands	None.....	After eleven months' treatment, no improvement in heart or vocal condition
2	28	F	Mitral stenosis	Ten years ago heart disease following scarlet fever; for the last 2 years had recurrent attacks of breaking compensation, and one morning during a cardiac attack awoke with voice "broken"; this lasted 10 days and became normal followed by recurrences preceded by cardiac symptoms; last one remained 3 weeks (until death); edema, cyanosis, enlarged liver	.....	.....	Recurred with breaking of compensation	No change	Dilated left auricle; no enlarged glands	Dilated left auricle; fibrous tissue causing strong adhesion between left auricle, aorta, esophagus and left bronchus; left auricle filled with clots; right ventricle large	
De Haviland Hall	19	F	.....	Heart disease of rheumatic origin	Right radial pulse larger than left	.....	.....	.....	Dilated heart	None.....	Right pupil larger than the left
Lian and Marcolles	42	F	Mitral stenosis	Heart disease of rheumatic origin for 20 years; the last 2 years had two cardiac crises with right hemiplegia; 5 months after last attack began to get hoarse at certain moments, in few months voice improved, but this was due to accommodation of right cord	Small, regular	.....	Improved with improvement of heart condition	.....	Dilated auricle; dilated and pulsating pulmonary artery; degree of mediastinitis, particularly in neighborhood of pulmonary artery	None.....	Partial paralysis of left vocal cord
Permewan 1 (Dr. N. Raw)	..	..	Mitral stenosis	....	.....	.....	.....	.....	....	Enormously dilated heart...	Brief verbal report

	2	..	..	Patent foramen ovale	.....	.....	.....	.....	.....	.....	Enormously dilated heart...	Brief verbal report
Guttman and Neuhoff	1	25	F	Mitral stenosis	Heart disease of rheumatic origin since 3 years; hoarseness 3 months ago; dry pericarditis, 3 weeks later evidence of fresh pericarditis over pulmonary area; dyspnea and palpitation but no edema	Blood pressure: right brachial 110/80, left brachial 82/70; right popliteal 118/85, left popliteal 105/70	.....	.....	.....	Dilated left auricle and pulmonary artery, aorta somewhat dilated	None	
Rosenthal	1	4½	F	Mitral stenosis; aortic stenosis	Six weeks after onset of rheumatic (?) fever, dyspnea, etc.; 2 weeks after fever, hoarseness, dyspnea, cyanosis, palpitations	.....	.....	.....	.....	Heart markedly enlarged	None.....	Patient died in a few weeks
		27	M	Mitral stenosis and insufficiency	For past 4 years difficulty in breathing; during the last year severe cardiac attacks, and lately dyspnea, cough, palpitations and edema; hoarseness developed while in hospital	.....	.....	.....	.....	Right and left-sided cardiac dilatation	None	
Carlau		16	F	Mitral stenosis	Four years ago onset of cardiac disease of rheumatic origin; decompensation 2 years ago; improved; well until 1 year later when, while walking, suddenly lost voice	.....	.....	.....	Voice better when patient is standing up than when lying down	Dilated auricle and right ventricle; some tracheobronchial glands	None.....	Improvement on digitalis treatment
Frestrolt and Stranz		..	..	.....	.....	.....	.....	.....	.....	.....	.....	Details not available
S. Gillies. ...		..	..	.....	.....	.....	.....	.....	.....	.....	.....	Details not available
Davis.....	1	40	F	Mitral stenosis	Five years ago lost voice which became normal after 2 months; 2 years ago bronchitis with loss of voice, since then no change in voice	.....	.....	After 3 years	.....	Heart dilated and displaced to the left; opaque posterior mediastinum	None.....	Patient living; more or less complete paralysis of left cord
	2	19	M	Mitral insufficiency, acute endocarditis and pericarditis	One year ago heart trouble; voice weak and hoarse; 6 months later convalescent but paralysis complete	.....	.....	.....	.....	No details given	None.....	Patient improved; compensation by right cord
Shuster.....		..	..	.....	.....	.....	.....	.....	.....	.....	.....	Details not available
Garland and White	1	27	M	Mitral stenosis	Athletic until 2 years ago; rheumatic heart disease; 6 months ago, caught cold and became hoarse; hoarseness persisted with remissions; at same time dyspnea on exertion compelled him to stop work 17 weeks ago; cyanosis	Equal, synchronous, regular	.....	Remissions reported	.....	Dilated left auricle; peribronchial thickening with enlarged bronchial glands	None.....	Right pupil larger than left; discharged; under observation two years, improved, but hoarseness persists

Analysis of the Reported Cases—(Continued)

Reporter	Patient		Heart Lesion	Brief History	Pulses	Pulsation at 2d Cartilage	Recurrent Paralysis	Change of Voice on Position	Roentgen Ray	Necropsy	Remarks
	Age	Sex									
2	53	F	Mitral stenosis	Heart disease since 6 years; worse last 2 years; 6 months ago hoarseness began to appear gradually and has persisted; cyanosis; large liver	Equal, irregular	...	.....	.....	.....	None.....	Discharged against advice; not heard from
3	48	F	Mitral stenosis, auricular fibrillation	Heart disease of rheumatic origin for past 7 years; deep cyanosis; large liver; edema	Irregular	...	.....	.....	Heart enlarged; bulging in region of left auricle	None.....	Electrocardiogram-fibrillation, right ventricular preponderance
4	40	F	Mitral stenosis; sclerosis of aorta and pulmonary artery	For 15 years heart disease of rheumatic origin; 9 months ago edema, etc.; in bed since; 5 days ago hoarse, slight cyanosis, edema	Absolute arrhythmia	...	.....	.....	Hydropneumothorax; heart displaced to left	Mitral stenosis; hydropericardium; arteriosclerosis of aorta and pulmonary artery; chronic pleuritis	Right pupil larger than left
5	12	M	Mitral stenosis and insufficiency	Heart disease since 2 years; cough with expectoration; dyspnea, palpitation, edema and hoarseness; large liver; pericarditis	.....	.....	.....	.....	Dilated heart; limited excursion; adherent pericarditis	None.....	Partial paralysis of left cord; patient died
6	26	F	Mitral stenosis	Sudden onset of heart disease 3 years ago, since then dyspnea on exertion, often orthopnea; 10 months ago hoarse following bronchitis; light cyanosis and edema of shins	.....	.....	.....	.....	Right and left heart enlarged; bulging of heart shadow at 2d interspace which does not correspond to aortic arch and is probably left auricle	None.....	First and second sounds reduplicated; complete paralysis of left cord; discharged unrelieved
7	12	M	Mitral stenosis and insufficiency; Adherent pericarditis (?)	One year ago, fever, dyspnea, palpitation, orthopnea	.....	.....	.....	.....	General enlargement of heart shadow, especially of left side	None.....	Left cord completely paralyzed
8	15	F	Mitral stenosis and insufficiency; Adherent pericarditis (?)	Two years heart disease, and dyspnea on exertion since, worse the last 4 months, edema of feet and hoarseness; cyanosis; large liver; "compensation poor;" died 1 year later	Small, absolutely irregular	...	.....	.....	General enlargement of heart shadow	None.....	Left cord completely paralyzed
9	22	F	Mitral stenosis; aortic insufficiency	Six months ago had cold with blood stained sputum; 2 months ago lost voice but was hoarse some time before this; decompensation followed	Synchronous	...	.....	.....	Heart dilated, both auricular regions prominent	None.....	Patient discharged unrelieved

Onset and Course of Hoarseness.—In some of the reported cases the onset of hoarseness was sudden, often occurring in the course of a walk. In all of such instances the onset occurred simultaneously with dyspneic attacks. Carrau, however, reported a case in which the patient had "the crisis of her heart disease without paralysis, and only six months before the termination of the crisis and without indication of the broken heart compensation, she lost her voice." Most of these patients show a rapid improvement to normal which may or may not be permanent. But they may show one or more recurrences coincident with cardiac crises, and the paralysis may finally become permanent in a complete or partial form.

In most cases, however, hoarseness comes on gradually. Its course is usually slow and progressive until a maximum is reached and remains permanent irrespective of cardiac improvement.

A few patients show marked improvement of the voice, the voice even becoming normal, but on examination it is found that this is not due to increased movement of the affected cord but to the accommodation of the sound one.

Change of position may, but does not always, influence the hoarseness. Proto found that in his patient rotation of the head in different positions produced a change in the voice. In Hofbauer's first case the voice became more hoarse with the patient lying on the left side or when bending forward. In the case of Lian and Marcolles the left lateral decubitus produced more marked hoarseness, while Carrau's patient showed a similar change when lying down in any position, but not on rotation of the head. All these cases were mild, and the onset was fairly rapid.

Hofbauer explained by Kraus' theory that in certain positions the aorta is pulled down more than in others, and hence stretching of the nerve is greater. The view of Lian and Marcolles is that in decubitus there is increased contact between the left auricle and the pulmonary artery and therefore between the latter and the nerve. Frestadtl and Stranz take exception to the reports of alteration in the quality of the voice with postural changes, because in their cases in which postmortem examination was made they found degeneration of the nerve and of the muscles supplied by that nerve, and therefore change of the voice was impossible. But it is clear from the facts given above that all cases of paralysis are not similar, since their onset and course and probably their etiology, differ. When the onset is gradual and progressive with degenerative changes in the nerve, vocal changes with posture cannot occur; whereas it is probable that paralyses of sudden onset and rapid improvement are due to a neuritis caused by mechanical disturbance in the mediastinum (as by the continuous pulsation of the pulmonary artery against the nerve, etc.), thus making the nerve more

sensitive to pressure, which varies on change of position, and with the change in pressure, alteration in the character of the voice occurs. This view corresponds to that of Lian and Marcolles, who explain recurrence of paralyses with cardiac crises by the pressure of the acutely enlarged heart upon the sensitive nerve.

The duration of hoarseness varies with the type of paralysis. Where it is acute and due at least partly to a neuritis, it improves in from a few days to two or three months, provided the cardiac condition improves and pressure paralysis does not supervene. When paralysis is complete, there is no change in the voice except so far as the sound cord can compensate. These facts are borne out by necropsy reports. The cases of Ortner, Osler (Case 3), Kraus and Von Schroetter, with permanent paralysis lasting for a year or more before death, showed microscopic degeneration of the nerve; that of Mead with paralysis of one month's duration showed no degeneration.

Quadrone reports seven cases in which there was bilateral paresis. He explains by Kraus' theory that where the descent of the aortic arch is so great as to affect the right subclavian vein, the right recurrent nerve becomes stretched in the descent of that vein. Ceraulo also reports a case of double paralysis.

DIAGNOSIS

An interesting and important point is the differentiation of these cases from aortic aneurysm, and undoubtedly such cases were diagnosed as aneurysm before the aid of the roentgen ray and before Ortner pointed out a hitherto unknown etiology.

Ortner, Nothnagle and Osler, in their first cases, made a diagnosis during life of aortic aneurysm, and only at necropsy was the true condition revealed. Ortner laid stress on the difference in the carotid pulses, the left being smaller than the right. Osler's opinion was influenced mainly by symptoms of dyspnea and cyanosis without edema and the presence of a diffuse precordial impulse reaching to the second intercostal space.

The difference in pulses has been noticed in other cases. Alexander, Hall, Ceraulo, Quadrone, and Fetterolf and Norris found the left pulse smaller than the right. Dmitrenko, and Guttman and Neuhoff noted that the blood pressure in the right brachial artery was greater than in the left.

Quadrone explains this difference to be due to traction on and constriction of the right subclavian artery. Ortner could not explain it, while Popoff states that it is due to pressure of a contracting cicatrix on the larger vessels.

A misleading sign is the cardiac pulsation in the area of the second costal cartilage. This may spread to the third and fourth spaces. Nine

of the reported cases show this condition. Alexander, Dmitrenko, Lian and Marcolles and others by tracings and radioscopic examinations have been able to demonstrate intra vitam that this pulsatile shadow was due to the pulsations of the pulmonary artery, which in many cases was found to be enlarged to the diameter of the aorta and even larger.

Inequality of pupils which is sometimes present strengthens the suspicion of aneurysm. Three cases are reported with the right pupil larger than the left and two with the left larger than the right.

Carrau diagnosed pressure of a dilated auricle on the pulmonary artery by the presence of systolic souffle propagated upward at the pulmonary area.

The difficulty of diagnosis is readily seen, and, with the presence of abnormal dulness about the second and third spaces, as found by Perotta and others, the picture of aneurysm is complete. We have therefore often to depend almost entirely on the roentgen ray for diagnosis in these cases.

AGE AND SEX

De Haviland Hall pointed out that aneurysm is rare before the age of 25, and in women it is one eighth as frequent as in men. From the tables of Avellis, Permewan points out that paralysis of the recurrent nerve due to various causes occurs more than twice as frequently in men as in women. In the list of cases of paralysis of the nerve in mitral stenosis twenty are male and forty-three female and according to the age period, distributed as shown below:

Age	Up to 25	25-30	30-40	40-50	50-55
No. of cases	20	30	10	8	2

From this it may be seen that the age and sex of the patient may be an aid in diagnosis. If the patient with paralysis of the left recurrent laryngeal nerve is a male and below 25, the paralysis is probably due to a cardiac cause, and also in females even if above 25 years of age.

TREATMENT

Digitalis in the early stages, before the nerve becomes degenerated, is useful in distinguishing between cardiac and aneurysmal compression. In Carrau's case with sudden hoarseness immediate use of digitalis produced excellent results, both cardiac and vocal conditions improving considerably. Of course when the paralysis is of long standing such improvement is impossible.

CONCLUSIONS

It is clear that paralysis of the recurrent laryngeal nerve in mitral stenosis may be produced in various ways, and that in a single case there may be more than one etiologic factor.

It seems probable that the most important and most frequent mechanism is that of the enlarged pulmonary artery, through its own dilatation, or through the pressure transmitted to it by the left auricle and pulmonary vein, compressing the nerve against the aorta or ductus arteriosus.

Secondary factors may aid in the compression by increasing the rigidity of the opposing parts, namely, thrombi in the auricle, thrombosis of the pulmonary artery, atheroma and sclerosis of the pulmonary artery and aorta, cicatrization, etc.

In a certain number of cases there is probably an initial neuritis, and if the cardiac condition is not improved, the irritability and the increased pressure would the more readily lead to degeneration of the nerve.

Cases occur in which the etiologic factor is enlarged mediastinal glands, etc., coincident with mitral stenosis, but even in these cases the heart may play a secondary part.

The importance of fluoroscopic examination must be emphasized, since it often affords the only distinction from aortic aneurysm.

The early use of digitalis both from the point of view of diagnosis and treatment is important.

It is interesting to note the comparative youth of the majority of the patients and its greater frequency in females, both of which observations are an aid in diagnosis.

Laryngoscopic examinations are important in eliminating any local cause of hoarseness, in making out the extent of paralysis, and in determining whether improvement of the voice is due to improvement of paralysis or to the accommodation of the sound cord.

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THE CREATININ TEST FOR RENAL FUNCTION*

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In a previous communication,[1] attention was directed to certain advantages in the use of creatinin as a test for renal function. This substance, which is apparently an end-product of metabolism, is excreted by the normal kidney with great ease; and its excretion, as emphasized by Schaffer,[2] is remarkably constant for the same person.

In the series of cases reported, it was pointed out that while normal kidneys responded promptly to an excess of creatinin in the circulation by a greatly increased urinary output of creatinin, the kidneys in chronic nephritis showed no such marked increase, and at times even showed a decrease. As a convenient method of studying the creatinin excretion, the patient's urine was first collected for the period of one hour and the patient then given 0.5 gm. of creatinin intravenously. Subsequent collections of urine were made at the end of one hour and at the end of two hours, and the total excretion of creatinin in each of these specimens compared with the hourly excretion before the patient received the creatinin injection.

In this study the same general method has been followed, but in addition observations have been made on the variations in the concentration of creatinin in the urine; the excretion of creatinin during fifteen minute periods has also been studied. In all instances, for the sake of comparison, the phenolsulphonephthalein test has been employed.

Some of the cases reported previously are included in the statistical summary in this paper. In all, the creatinin test has been carried out on 113 persons, including thirty-three with cases of chronic nephritis, thirty with arterial hypertension, seven with marked cardiac decompensation and twenty-five with diabetes mellitus.

METHODS

In most of the earlier tests the creatinin was prepared fresh before using, 0.5 gm. being dissolved in 5 c.c. of distilled water and autoclaved just before injection. In some of the later tests we have used creatinin dissolved in a buffer solution consisting of 27 parts of primary potas-

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sium phosphate and 73 parts of secondary sodium phosphate, having a p_H value of 7.2. In this solution, a colorimetric reading shows no deterioration of the creatinin for a period of six months. We have found it convenient to put up such a solution in ampules of 5 c.c., each ampule containing 0.5 gm. of creatinin and being ready for immediate use.

The creatinin content of the urine has been determined by the method of Folin, using in most instances a Dubosc colorimeter. The simple colorimeter devised by Myers [3] has also proved satisfactory for the estimation of creatinin.

In the majority of the tests, the first hour's and the second hour's excretion of creatinin after the intravenous injection of 0.5 gm. of creatinin has been compared with the excretion for one hour before the injection. In another series of tests the excretion of creatinin over fifteen minute intervals after injection has been compared with the

TABLE 1.—*Average Creatinin Excretion in Normal and in Diseased Persons*

Group	Creatinin Excretion	One Hour Before Injection	First Hour After Injection	Second Hour After Injection
Normal	Total in milligrams	64	214	113
	Milligrams per 100 c.c.	158	346	195
Cardiac diseases	Total in milligrams	42	127	107
	Milligrams per 100 c.c.	100	283	180
Diabetes mellitus	Total in milligrams	57	168	130
	Milligrams per 100 c.c.	115	215	110
Arterial hypertension	Total in milligrams	49	159	96
	Milligrams per 100 c.c.	134	286	189

excretion for a period of fifteen minutes before. The latter method has not proved reliable unless the urine is collected by catheter, but it may find a useful application when it is necessary to carry out the test in a short time and when it is desirable to study the excretory function of each kidney separately.

It is necessary in all tests to use extreme care that the bladder is emptied completely at the time of each collection of urine. To promote as free a flow of urine as possible, the patient is given a glass of water (150 c.c.) after each voiding.

The Excretion of Creatinin at Intervals of One Hour.—Twelve normal persons were first studied and then the results obtained in patients suffering from a variety of diseases, this series including five cases of cardiac decompensation, ten cases of diabetes mellitus and twenty cases of arterial hypertension. The average excretion in this group is shown in Table 1.

3. Myers, V. C.: A Simple Colorimeter for Clinical Purposes, J. Lab. & Clin. Med. **1**:760, 1916.

This table shows that in this series the total excretion of creatinin one hour after injection is more than twice that of the hour preceding injection, and if the cardiac group is excluded, the excretion at the end of one hour is three times as great as before injection. The total excretion of creatinin at the end of the second hour also averages more than twice that of the hour preceding injection, although in some groups it falls slightly below this average.

The excretion of creatinin in milligrams per hundred cubic centimeters, which is an index of the concentrating ability of the kidneys, at the end of one hour is more than twice that of the hour preceding injection, while at the end of the second hour the increase is not so great.

TABLE 2.—*Creatinin Excretion in Twenty-Five Cases of Chronic Nephritis After Injection of Creatinin* *

	Blood		Before Injection		1 Hour After Injection		2 Hours After Injection		Phenolsulphonephthalein	
	Urea	Creatinin	Total	Per 100 C.c.	Total	Per 100 C.c.	Total	Per 100 C.c.	Percentage	Remarks
1	22	1.8	70	50	68	71	71	94	43	
2	16	1.5	27	183	8	98	38	224	40	Died later of uremia
3	81	5.0	36	70	7	18	19	50	7	
4	12	1.7	30	123	54	129	50	100	18	Died 6 months later
5	20	1.0	56	70	0	0	142	54	40	
6	11	2.0	16	30	12	27	12	26	Trace	Died; necropsy
7	26	1.5	91	201	122	102	95	95	30	
8	46	2.7	45	90	46	70	70	47	Trace	Died; necropsy
9	13	1.2	37	83	17	105	31	118	50	
10	14	2.3	43	112	63	180	66	300	40	
11	17	2.8	138	153	179	256	44	145	22	
12	20	2.0	30	106	39	133	25	100	15	Died 3 months later
13	22	1.5	25	125	9	44	40	116	25	
14	46	4.2	48	44	60	47	64	58	3	Died 2 months later
15	25	2.6	86	284	155	125	119	61	30	
16	37	1.5	75	35	88	42	60	50	15	
17	60	2.4	50	90	55	109	80	267	15	Died; necropsy
18	81	7.0	17	58	26	58	25	62	5	Died; necropsy
19	21	1.5	75	108	57	320	53	534	..	Died; necropsy
20	40	6.6	99	142	118	157	198	222	7	
21	37	2.8	32	71	8	50	50	105	6	
22	15	1.5	74*	124	109	218	110	200	35	
23	15	1.9	91	118	121	328	118	454	45	Died 2 months later; necropsy
24	35	2.3	80	100	102	164	35	69	12	
25	32	2.0	74	41*	92	77	63	63	45	

* Urine was collected at one hour intervals. Creatinin excretion is expressed in milligrams; blood urea and blood creatinin are expressed in milligrams per 100 c.c.

A study of the group of twenty-five cases of chronic nephritis shows a very different behavior in the excretion of creatinin following injection. This group is of especial interest, and the results are charted in some detail in Table 2. All of these patients were clear-cut examples of patients with chronic nephritis, and an arterial hypertension was present. Six of the patients came to necropsy. One patient died while under observation, but necropsy was not performed, and three patients died after discharge from the hospital.

A study of this table shows that in chronic nephritis the kidneys do not respond to the increased creatinin content of the blood by an increase in the output amounting to two or three times that excreted before

injection. In eight patients the total amount of creatinin excreted during the hour period after injection was less than the amount excreted during the hour before injection. This is a striking finding and indicates that while the normal kidney responds promptly to the increased amount of creatinin in the blood, this increase may in disease exert a partially paralyzing effect on the kidney so that it excretes less than before (Fig. 1).

The excretion of creatinin in terms of milligrams per 100 cubic centimeters follows much the same course in these cases of chronic

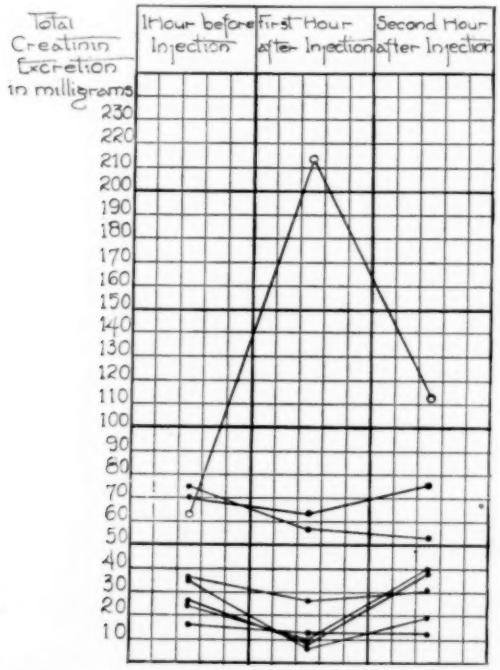

Chart 1.—Creatinin excretion in seven cases of chronic nephritis. Note depression following intravenous injection of creatinin. A curve showing the average excretion in twelve normal controls is superimposed on the table. The line and hollow dots indicate the average normal excretion; the line and solid dots indicate chronic nephritis.

nephritis as does the total excretion. Here again the average creatinin concentration in the urine is only slightly increased one hour after the injection, and in eight instances it was actually less than before.

The phenolsulphonephthalein excretion in most of these patients was markedly decreased, although there were a few exceptions. Patient

No. 2, who excreted 40 per cent. in two hours, died two weeks later of uremia; and Patient No. 23, who excreted 45 per cent. phenolsulphonephthalein in two hours, died two months later. Both of these patients showed the nephritic type of creatinin curve, and the diagnosis of chronic nephritis was confirmed by necropsy in Patient No. 23.

A comparison between the type of curves obtained in chronic nephritis and those in other conditions is shown in Charts 1 and 2.

The Excretion of Creatinin at Intervals of Fifteen Minutes.—In order to shorten the time necessary for carrying out the creatinin test, a series of observations were made on patients, examining the urine at

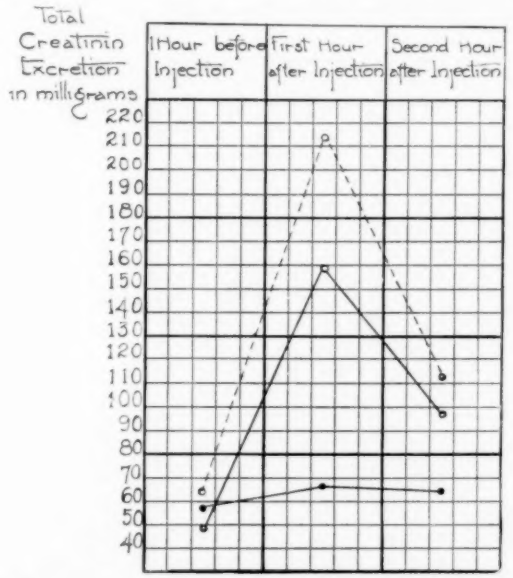

Chart 2.—Average total creatinin excretion in three groups of cases; hour periods. The broken line and hollow dots indicate normal; the continuous line and hollow dots, arterial hypertension; the continuous line and solid dots, chronic nephritis.

quarter hour periods instead of at the end of each hour. It was found early in the use of this method that slight delays in the collection of the urine or failure to empty the bladder completely made the results inaccurate. In order to avoid these sources of error, we catheterized our patients, and the catheter was kept in the bladder until the conclusion of the test.

This series comprises a smaller group of cases consisting of eight cases of chronic nephritis, ten cases of arterial hypertension and eight cases of diabetic mellitus. The urine in each instance was collected

first for fifteen minutes, then 0.5 gm. creatinin was injected intravenously and the urine collected at fifteen minute periods for one hour. The patient received a glass of water (150 c.c.) fifteen minutes before each collection of urine. The results in terms of total creatinin excretion are shown in Figure 4, while the ability of the kidney to concentrate and excrete the creatinin is shown in Figure 5.

A study of the curve of total creatinin excretion shows that using fifteen minute periods of observation, the kidneys in chronic nephritis are unable to respond to the intravenous injection of creatinin by any marked increase in excretion. In the two other conditions studied which were accompanied by no evidence of renal lesions, the injection

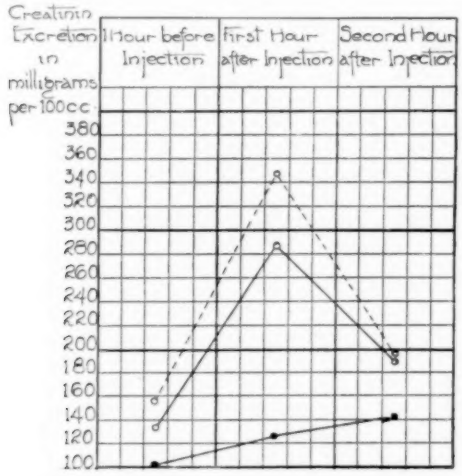

Chart 3.—Average excretion of creatinin in milligrams per 100 c.c. of urine, in same patients as in Chart 2. The broken line and hollow dots indicate normal; the continuous line and hollow dots, arterial hypertension; the continuous line and solid dots, chronic nephritis.

of creatinin was followed by a marked increase in output, the average for the first fifteen minute period after injection being three times that of the same period before injection.

The curve of urinary creatinin concentration in Figure 5 shows that while patients with diabetes and arterial hypertension respond with an immediate marked increase in concentration, followed by a fall, the nephritic patients show marked delay in this response.

This method of studying the creatinin excretion in fifteen minute periods is being used at this clinic for certain selected cases. While our experience with it is not as great as with the method of hourly collec-

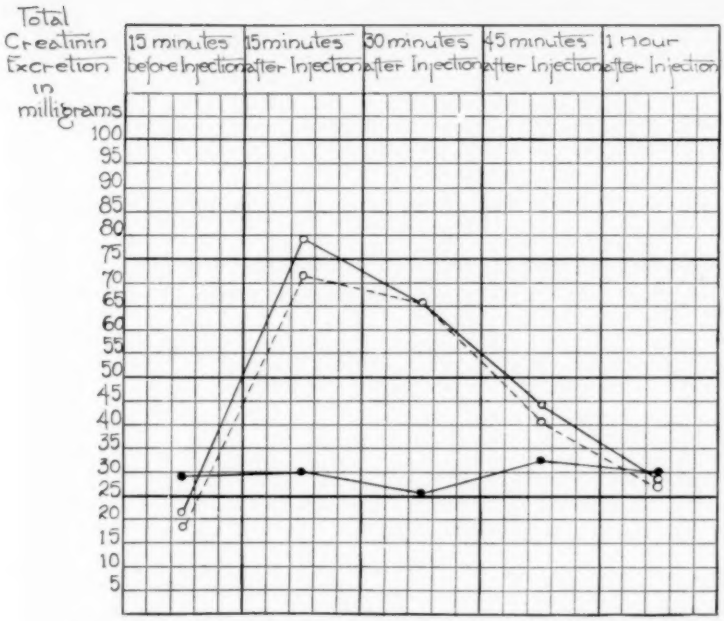

Chart 4.—Average total creatinin excretion over fifteen minute periods. The solid line and hollow dots indicate arterial hypertension; the broken line and hollow dots, diabetes mellitus; the continuous line and solid dots, chronic nephritis.

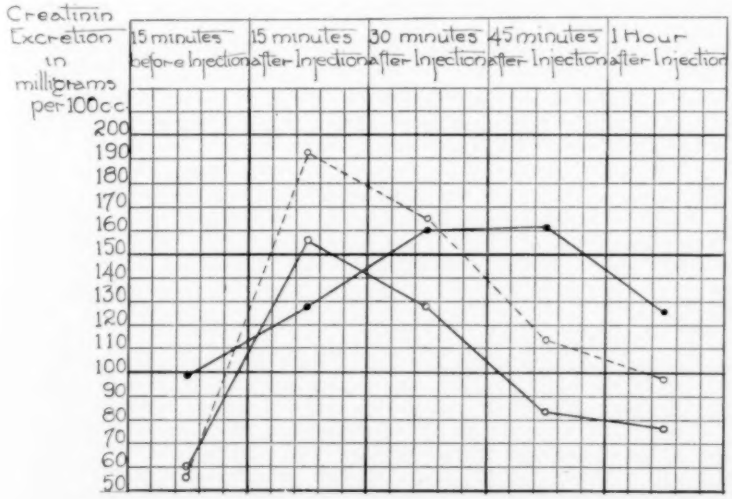

Chart 5.—Average excretion of creatinin in milligrams per 100 c.c. of urine over fifteen minute periods; same patients as in Chart 4. The broken line and hollow dots indicate diabetes mellitus; the continuous line and solid dots, chronic nephritis; the continuous line and hollow dots, arterial hypertension.

tions, it appears to be reliable when properly carried out, and may prove of great value in studying the functional capacity of the individual kidney.

CONCLUSIONS

The creatinin test as described in this paper has proved to be a good index of kidney function in disease.

The normal kidneys respond to the intravenous injection of creatinin by an increased output of creatinin which averages three times that excreted during the same period of time.

The kidneys in chronic nephritis show on the average only a slight increase. In many instances a decrease was observed.

THE EXCRETION OF ORGANIC ACIDS IN THE URINE OF PATIENTS WITH DIABETES MELLITUS *

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Several observers have described cases of diabetes mellitus in which there appeared to be severe acidosis but in which there was no evidence in the urine of the presence of acetone bodies. Such cases have been described, for example, by Stadelmann [1] in 1883, by Frerichs [2] in 1884, by Lépine [3] in 1909, by Revillet [4] in 1914, by Rosenbloom [5] in 1915, by McCaskey [6] in 1916, and more recently by Bock, Field and Adair [7] in 1923. These isolated observations have suggested the possibility that other acids than the acetone bodies may play a part in the production of diabetic acidosis, and have led us to study the urine of a series of diabetic patients to determine whether other organic acids than the ketones are ever excreted in any significant amounts. This paper records the results of this work.

We have used the following method: Mixed twenty-four hour samples of urine preserved with toluol or fresh single specimens were used for each analysis. The total organic acid concentration was determined by the method of Van Slyke and Palmer.[8] The acetone body concentration, including acetone, diacetic and beta-hydroxybutyric acid, was determined by the gravimetric method of Van Slyke.[9] From these analyses we were able to fraction the organic acidity of any urine into two parts; the first fraction being the one due to the acetone bodies, and the second being due to undetermined organic acid or acids. In several samples we determined the creatin and creatinin content by Folin's [10]

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

1. Stadelmann, E.: Ueber die Ursachen der pathologischen Ammoniakausscheidung beim Diabetes Mellitus und des Coma diabeticum, Arch. f. experimentelle Pathol. **17**:419-444, 1883.

2. Von Frerichs, F. T.: Ueber den Diabetes, Berlin, August Hirschwald, 1884, p. 113.

3. Lépine, R.: Le diabète sucré, Paris, Alcan, 1909.

4. Revillet: Coma chez une diabétique sans acétonurie, Lyon med. **122**:817, 1914.

5. Rosenbloom, J.: A Form of Diabetic Coma, Not Due to the Acetone Bodies, New York M. J. **102**:294-296 (Jan. 29) 1915.

6. McCaskey, G. W.: A Case of Fatal Diabetic Coma Without Diacetic or Beta-Oxybutyric Acid, J. A. M. A. **66**:350-351, 1916.

7. Bock, A. V.; Field, H., Jr., and Adair, G. S.: The Acid Base Equilibrium in Diabetic Coma, In press.

8. Van Slyke, D. D., and Palmer, W. W.: The Titration of Organic Acids in Urine, J. Biol. Chem. **41**:567-585, 1920.

9. Van Slyke, D. D.: The Determination of B-Hydroxybutyric Acid, Aceto-Acetic Acid, and Acetone in Urine, J. Biol. Chem. **32**:455-493, 1917.

10. Folin, O.: Laboratory Manual of Biological Chemistry, New York, D. Appleton & Co., 1922.

method, as Van Slyke and Palmer point out that these substances may interfere with the total organic acid excretion obtained by their method. We did not find, however, that this analysis was necessary in every case, as the highest creatin and creatinin figures encountered in the

TABLE 1.—*The Organic Acid Excretion in the Urine of Patients with Diabetes Mellitus* *

	C.c. N/10 Acid per Liter				C.c. N/10 Acid per Liter		
Sample No.	Total Organic Acid	Total Acetone	Undetermined Acid	Sample No.	Total Organic Acid	Total Acetone	Undetermined Acid
1	1,750	1,380	370	51	620	470	150
2	1,740	1,450	290	52	600	420	180
3	1,480	1,140	340	53	600	350	250
4	1,420	1,140	280	54	600	360	240
5	1,370	1,050	320	55	590	430	160
6	1,320	1,140	180	56	580	410	170
7	1,280	980	300	57	580	150	430
8	1,220	1,040	180	58	580	170	410
9	1,230	1,000	230	59	580	320	260
10	1,180	870	310	60	550	370	180
11	1,180	905	275	61	540	170	370
12	1,170	790	380	62	540	170	300
13	1,110	770	340	63	500	290	210
14	1,080	910	170	64	500	260	240
15	1,060	910	150	65	480	130	350
16	1,040	840	200	66	480	160	320
17	1,020	850	170	67	480	210	270
18	980	800	180	68	460	70	390
19	970	800	170	69	440	240	200
20	970	690	280	70	440	270	170
21	960	650	310	71	420	270	150
22	960	820	140	72	420	270	150
23	960	670	290	73	420	60	360
24	960	790	170	74	420	60	340
25	940	770	170	75	410	300	110
26	910	570	340	76	400	170	230
27	910	570	210	77	400	200	200
28	900	825	75	78	400	125	275
29	800	600	170	79	380	140	240
30	840	700	140	80	380	100	280
31	820	670	150	81	370	190	180
32	820	500	320	82	370	180	190
33	800	710	90	83	360	180	180
34	800	700	100	84	320	80	240
35	800	550	250	85	320	40	280
36	780	410	370	86	300	100	200
37	760	610	150	87	290	110	180
38	750	430	320	88	280	50	230
39	720	480	240	89	280	200	80
40	720	470	250	90	260	40	220
41	720	460	260	91	250	25	225
42	700	310	390	92	250	50	200
43	700	340	360	93	220	60	160
44	700	570	130	94	220	0	220
45	680	300	380	95	220	70	150
46	670	450	220	96	200	40	160
47	670	420	250	97	200	20	180
48	670	500	170	98	200	10	190
49	660	440	220	99	190	35	155
50	640	300	340	100	170	70	100
Average							233

* Urines in which the undetermined fraction was less than 450 c.c. per liter.

urines containing most nitrogen did not account for any large proportion of the total urinary acidity. We expressed our results in terms of decinormal organic acid or total acetone per liter of urine.

We analyzed in this fashion a series of 114 urine samples obtained from eighteen diabetic patients with varying degrees of acidosis, divid-

ing the results into two groups. Group 1 contains those urines of varying degrees of acidity in which the undetermined organic acid fraction was 450 c.c. or less per liter. Group 2 contains those diabetic urines of varying degrees of acidity in which the undetermined organic acid fraction was more than 450 c.c. per liter. We divided our results in this arbitrary fashion because Van Slyke and Palmer's figures for thirteen normal men show that the average normal organic acid excretion does not exceed 450 c.c. per liter of urine. The results of these analyses are recorded in Tables 1 and 2.

As can be seen by Table 1, 100 of the 114 samples of urine, or 88 per cent., had an unidentified organic acid excretion of less than 450 c.c. to the liter. In this series the unidentified acidity varied between 430 and 75 c.c. to the liter, while the average was 233 c.c. Those urines with the highest total acidity contained the most acetone bodies, and the

TABLE 2.—*The Organic Acid Excretion in the Urine of Patients with Diabetes Mellitus* *

	C.c. N/10 Acid per Liter		
Sample No.	Total Organic Acid	Total Acetone	Undetermined Acid
1	2,970	40	2,930
2	1,620	1,100	520
3	1,540	870	670
4	1,460	885	575
5	1,460	860	600
6	1,440	945	495
7	1,380	150	1,230
8	1,160	675	485
9	1,130	430	700
10	1,100	220	880
11	900	0	900
12	880	140	740
13	800	330	470
14	610	109	501

* Urines in which the undetermined fraction was more than 450 c.c. per liter.

parallelism between the excretion of the total organic acids and acetone bodies was striking. Van Slyke and Palmer have already mentioned that the organic acid titration in diabetic urines is so parallel to the acetone body analyses that the rise above the normal output in organic acid excretion may be used as an approximate measure of the acetone body excretion. So far as we can determine from the literature, the method has not come into general clinical use in this country for this purpose except at the Montreal General Hospital, where Rabinovitch [11] reports satisfactory results with it. Our data show that by subtracting the average undetermined acid figure of 230 from any one of the total organic acid readings, we obtained a fair index of the total acetone concentration, especially in cases in which this was high enough to be of any clinical significance. This point is important for people doing

11. Rabinovitch, I. M.: A Simple Method for Determining the Approximate Degree of Acidosis in Diabetes Mellitus, Canad. M. J. **11**:526-528, 1921

routine diabetic laboratory work, as the organic acid titration is simple and easy to perform, whereas the total acetone estimation is more time consuming and requires more apparatus.

Table 2 records the fourteen urine samples from four cases which contained more than 450 c.c. of unidentified organic acid to the liter. The unidentified fraction varied from 485 c.c. to 2,930 c.c. The urine of one of Van Slyke and Palmer's normal men contained 740 c.c. of tenth normal organic acids to the liter. If we exclude all the urines in Table 2 with readings below this point on the ground that they might contain no more than normal amounts of acid, there still remain four samples from two cases of coma with so high a concentration of unidentified organic acid as to bring up the question whether such acid or acids may not have produced clinical symptoms of acidosis, and may not have played a part in producing the clinical picture of diabetic coma.

If other acids than the ketones produce diabetic acidosis, they should be recognizable not only in the urine but also should manifest themselves in the blood. Our next step, therefore, was the attempt to discover the presence of such acids by fractioning the acid content of the blood from cases with diabetic acidosis as we fractioned the acidity of the urine. For this purpose we have made use of an indirect method open to certain obvious objections, but one which has yielded interesting results.

Fitz and Van Slyke [12] estimated in their studies on the alkaline reserve and acid excretion that the acid retained in the blood could be rationally expressed by the following formula:

$$\text{Retained acid} = 80 - \text{plasma } CO_2.$$

They used this expression because they found that when the plasma carbon dioxid reached 80 volumes per cent. the urinary acidity to phenolphthalein and the ammonia excretion approached zero, while as the plasma carbon dioxid fell below this point the excretion of free and combined acids increased proportionally. From this they concluded that there was a definite relationship between acids retained in the blood and acids excreted in the urine and that when the blood carbon dioxid was 80 volumes per cent. there was a negligible amount of acid in the blood and therefore no excretion of acid in the urine.

Van Slyke, Stillman and Cullen [13] have demonstrated that the molecular concentration of carbon dioxid in any plasma can be found by dividing the volumes per cent. of carbon dioxid as determined by Van Slyke's method by 2,240.

12. Fitz, R., and Van Slyke, D. D.: The Relationship Between Alkaline Reserve and Acid Excretion, J. Biol. Chem. **30**:389-400, 1917.

13. Van Slyke, D. D.; Stillman, E., and Cullen, G. E.: A Method for Titrating the Bicarbonate Content of the Plasma, J. Biol. Chem. **38**:167-178, 1919.

Assuming that acids retained in the blood displace carbon dioxid in ratio to their molecular concentration, and accepting Fitz and Van Slyke's figures, the "retained acid" of the blood can be expressed as follows:

$$\text{Molecular concentration of retained acid} = 0.0357 - \frac{CO_2}{2,240}.$$

We used this formula and determined in this fashion the molecular concentration of the total "acid retained in the blood" in a series of fifty-two blood samples from twelve cases of diabetes. We obtained at the same time the molecular concentration of the acetone bodies in these bloods including acetone, diacetic acid and beta-hydroxybutyric acid by the gravimetric method of Van Slyke and Fitz:[14] thus we were able to fraction indirectly the "retained acid" of these bloods into two parts, the first fraction being the one due to the acetone bodies and the second being due to undetermined acid or acids.

We have arbitrarily divided the results of these analyses into two groups. The first group contains the bloods with an unidentified "retained acid" of concentration less than 0.0135 M. The second group contains the bloods with an unidentified "retained acid" of concentration greater than this figure. We have selected this figure as a dividing point because acetone free bloods with a carbon dioxid combining power of less than 50 volumes per cent. will necessarily have a "retained acid" of greater concentration than 0.0135 M, and plasmas with carbon dioxid capacities below this point are ordinarily supposed to be indicative of acidosis.

As can be seen forty-six bloods, or 88 per cent. of the samples studied, fall in Group 1, the average undetermined "retained acid" having a molecular concentration of 0.0072, the maximum "retained acid" being 0.0135 M and the minimum being zero. It is of interest, however, that the variation in unidentified "retained acid" should have been so relatively slight considering that the blood samples represented degrees of acidosis from 12.8 volumes per cent. of carbon dioxid to normal, and degrees of acetonemia from over 100 mg. of total acetone per 100 c.c. of blood to less than 10 mg. Furthermore, the average molecular concentration of "unidentified retained acid" was 0.0072 M, which would correspond to an alkali reserve of 80 — 16.1, or 63.9 volumes per cent., which is a normal figure.

Table 4 includes the six blood samples with an unidentified "retained acid" of a concentration greater than 0.0135 M. The figures vary between 0.0148 and 0.0205 M. They appear to be of greater significance if the effect of the "unidentified retained acid" on the plasma bicarbonate is estimated. The blood with the lowest undetermined "retained acid" represents one having an acidosis of 80 — 32.5, or 47.5 volumes

14. Van Slyke, D. D., and Fitz, R.: The Determination of B-Hydroxybutyric Acid, Aceto-Acetic Acid, and Acetone in Blood, J. Biol. Chem. **32**:495-497, 1917.

per cent. of carbon dioxid, a figure on the lower limits of normal. The blood having the highest undermined "retained acid" represents one having an acidosis of 80 — 46 or 34 volumes per cent. of carbon dioxid, a figure certainly low enough to be significant.

On the whole, we found from these preliminary observations that about 90 per cent. of a series of 114 diabetic urines contained unidentified acid or acids within the concentration limits of organic acids

TABLE 3.—*The "Retained Acid" in the Blood of Patients with Diabetes Mellitus* *

Number	Total "Retained Acid" Molecular	Total Acetone Bodies Molecular	Undetermined "Retained Acid" Molecular	Number	Total "Retained Acid" Molecular	Total Acetone Bodies Molecular	Undetermined "Retained Acid" Molecular
1	0.0334	0.0240	0.0094	24	0.0148	0.0108	0.0040
2	0.0304	0.0156	0.0108	25	0.0146	0.0084	0.0062
3	0.0285	0.0183	0.0102	26	0.0142	0.0125	0.0017
4	0.0277	0.0213	0.0064	27	0.0137	0.0088	0.0049
5	0.0269	0.0140	0.0129	28	0.0136	0.0071	0.0065
6	0.0240	0.0109	0.0131	29	0.0133	0.0072	0.0061
7	0.0227	0.0123	0.0104	30	0.0129	0.0112	0.0017
8	0.0221	0.0106	0.0115	31	0.0126	0.0057	0.0069
9	0.0219	0.0113	0.0106	32	0.0122	0.0047	0.0075
10	0.0206	0.0072	0.0134	33	0.0112	0.0038	0.0074
11	0.0200	0.0065	0.0135	34	0.0111	0.0046	0.0065
12	0.0194	0.0104	0.0090	35	0.0109	0.0046	0.0063
13	0.0187	0.0123	0.0064	36	0.0103	0.0084	0.0019
14	0.0185	0.0108	0.0077	37	0.0098	0.0038	0.0060
15	0.0182	0.0068	0.0114	38	0.0097	0.0015	0.0082
16	0.0156	0.0093	0.0063	39	0.0094	0.0044	0.0050
17	0.0156	0.0057	0.0099	40	0.0093	0.0053	0.0040
18	0.0152	0.0079	0.0073	41	0.0093	0.0027	0.0066
19	0.0151	0.0070	0.0081	42	0.0091	0.0073	0.0018
20	0.0151	0.0088	0.0063	43	0.0089	0.0050	0.0039
21	0.0151	0.0070	0.0080	44	0.0089	0.0042	0.0047
22	0.0151	0.0147	0.0004	45	0.0084	0.0029	0.0055
23	0.0149	0.0040	0.0109	46	0.0062	0.0053	0.0009

* Bloods in which the undetermined fraction was in a concentration less than 0.0135 M.

TABLE 4.—*The "Retained Acid" in the Blood of Patients with Diabetes Mellitus* *

Number	Total "Retained Acid" Molecular, per 100 C.c.	Total Acetone Bodies Molecular, per 100 C.c.	Undetermined "Retained Acid" Molecular, per 100 C.c.
1	0.0304	0.0099	0.0205
2	0.0304	0.0156	0.0148
3	0.0317	0.0126	0.0191
4	0.0295	0.0140	0.0145
5	0.0287	0.0108	0.0179
6	0.0198	0.0035	0.0163

* Bloods in which the undetermined fraction was in a concentration more than 0.0135 M.

present in normal urines. About 10 per cent., however, contained organic acid or acids other than the acetone bodies in considerably higher concentration than is ordinarily found in normal urines. About 90 per cent. of a series of fifty-two diabetic bloods contained acetone bodies of which the molecular concentration appeared to account for the diminution below 80 volumes per cent. of alkali reserve encountered, and in which therefore the unidentified "retained acid" fraction

was insufficient to produce acidosis. About 10 per cent. contained an alkali reserve which was far less than could be accounted for by the blood acetone body concentration present, and which therefore had an unidentified "retained acid" fraction which might be a factor in producing symptoms. These facts suggest that in certain cases of diabetic acidosis other acids than the acetone bodies are formed in the body in abnormal amounts and are excreted in the urine.

We have seen clinically at least six cases of diabetes which support this conclusion. Bock, Field and Adair have recently published one of these cases, and four others are reported here. The following case is first discussed by way of control. We believe that it represents the type of diabetic acidosis due solely to acetone bodies and is commonly encountered.

REPORT OF CASES

Case 1.—P. B. B. H., a woman, aged about 50, with diabetes of ten years' duration, entered the hospital Feb. 23, 1923, with a plasma carbon dioxid of 19 volumes per cent. and appeared critically ill. She was treated with insulin and ordinary dietetic management. The studies on acidosis which were made are recorded in Table 5.

Table 5.—*Acidosis in Case 1*

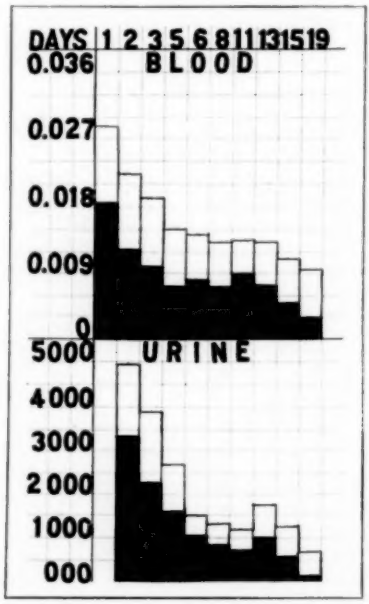
	Urine				Blood		
Date, 1923	Total Organic Acid. C.c. N/10 per 24 Hours	Total Acetone. C.c. N/10 per 24 Hours	Total Undetermined Acid. C.c. N/10 per 24 Hours	Total Nitrogen, Gm. per 24 Hours	Total "Retained Acid." per 100 C.c., Molecular	Total Acetone Bodies, per 100 C.c., Molecular	Total Undetermined "Retained Acid." per 100 C.c., Molecular
Feb. 23	.....	.....	.....	....	0.0284	0.0183	0.0101
24	4,850	3,300	1,550	13.3	0.0227	0.0123	0.0104
25	3,850	2,180	1,670	19.7	0.0194	0.0104	0.0090
27	2,640	1,650	990	10.7	0.0151	0.0070	0.0081
28	1,500	1,120	380	5.6	0.0147	0.0084	0.0063
March 2	1,300	860	440	4.7	0.0133	0.0071	0.0062
5	1,170	710	460	5.1	0.0137	0.0088	0.0049
7	1,740	960	780	5.6	0.0136	0.0071	0.0065
9	1,260	630	630	5.9	0.0111	0.0046	0.0065
13	640	140	500	4.4	0.0093	0.0027	0.0066

When the "retained acid" of the blood was highest, the excretion of organic acids was highest, and as the "retained acid" of the blood diminished so did the total acid excretion. There was a definite parallelism, also, between the blood acetone concentration and acetone excretion and between the undetermined "retained acid" of the blood and its excretion. These various relationships are shown graphically in the chart.

The fact that the nitrogen excretion was highest when the undetermined organic acid excretion was highest and that it fell as the undetermined organic acid excretion fell, suggests a possible interrelationship between protein catabolism and the acid or acids excreted. In this case the molecular concentration of undetermined "retained acid" in the blood never exceeded 0.0104 M. We do not consider, therefore, that this patient had an acidosis of sufficient degree to influence the alkali reserve caused by acids other than the acetone bodies in spite of the somewhat increased undetermined organic acid excretion during the first few days' observation. On the other hand, we believe that in this case the clinical signs of acidosis were due entirely to the acetone bodies. This case offers a sharp contrast to the four following cases.

Case 2.—A man, aged 49, entered the Massachusetts General Hospital on Feb. 2, 1920, in coma and died thirty-six hours later. By way of treatment he was given forced fluids, oatmeal gruel and orange juice. He did not receive alkali. The observations on acidosis obtained are given in Table 6.

As can be seen, the total "retained acid" of the blood increased as coma developed while the acetone fraction diminished. As a result, the undetermined "retained acid" in the blood increased to a point compatible with the production of clinical symptoms. The concentration of unidentified acids in the urine increased as judged by the titratable acidity plus the ammonia figure, while the concentration of acetone bodies in the urine diminished. It seems highly probable, therefore, that this patient died with an increasing acidosis of undetermined cause, the acetone bodies playing a minor part.



The "retained acid" of the blood and the excretion of organic acids in a case of severe diabetic acidosis. The columns represent the molecular concentration of the "retained acid" of the blood or the twenty-four hour excretion of tenth normal organic acids in urine. The solid columns represent the molecular concentration of acetone bodies in the blood or their excretion as tenth normal acid in urine. The white columns represent the molecular concentration of "unidentified retained acid" in the blood and the unidentified tenth normal organic acids excreted in the urine.

Case 3.—A man, aged 22, entered the Massachusetts General Hospital on Feb. 6, 1923, in coma and died about thirty hours later. By way of treatment he received forced fluids, oatmeal gruel and orange juice, sodium bicarbonate and insulin. The observations made on his blood and urine are given in Table 7.

The concentration of organic acids excreted in the urine increased steadily despite the fact that the acetone fraction diminished. Thus the undetermined

fraction grew steadily larger. At the first analysis the undetermined "retained acid" figure in the blood was abnormally high and remained elevated despite the fact that the acetone bodies disappeared from the blood. It is possible that the undetermined "retained acid" of the blood was actually greater than appears in the table because of the sodium bicarbonate given, as this would tend to lower the "undetermined retained acid" fraction of the "blood acidity" as we have estimated it. Despite the alkali taken, the patient was in acidosis at the time of death as the plasma carbon dioxid capacity was only 40 volumes per cent., and the acidosis was not due to the acetone bodies.

TABLE 6.—*Acidosis in Case 2*

	Urine			Blood		
Date, 1920	Total Organic Acid,* C.c. N/10 per Liter Urine	Total Acetone, C.c. N/10 per Liter Urine	Total Undetermined Acid, C.c. N/10 per Liter Urine	Total "Retained Acid," per 100 C.c., Molecular	Total Acetone Bodies, per 100 C.c., Molecular	Total Undetermined "Retained Acid," per 100 C.c., Molecular
February entry...	820	910	— 90	0.0281	0.0212	0.0069
24 hours.....	...	...	.....	0.0304	0.0198	0.0106
36 hours.....	853	550	+303	0.0804	0.0100	0.0204

* In this case the urinary acidity was not titrated by the method of Van Slyke and Palmer; it is the titratable acidity by Folin's method plus the c.c. of tenth normal ammonia.

TABLE 7.—*Observations on Blood and Urine in Case 3*

	Urine			Blood		
Feb. 6-8, 1923	Total Organic Acid, C.c. N/10 per Liter Urine	Total Acetone, C.c. N/10 per Liter Urine	Total Undetermined Acid, C.c. N/10 per Liter Urine	Total "Retained Acid," per 100 C.c., Molecular	Total Acetone Bodies, per 100 C.c., Molecular	Total Undetermined "Retained Acid," per 100 C.c., Molecular
Entry.....	1,100	675	485	0.0329	0.0183	0.0246
4 hours.....	.....	.....	.....	0.0279	0.0129	0.0150
14 hours.....	1,380	146	1,234	0.0219	0.0004	0.0205
30 hours.....	1,700	90	1,610	0.0179	0.0000	0.0174

TABLE 8.—*Blood and Urine Analyses in Case 4*

	Urine			Blood		
Date, 1923	Total Organic Acid, C.c. N/10 per Liter Urine	Total Acetone, C.c. N/10 per Liter Urine	Total Undetermined Acid, C.c. N/10 per Liter Urine	Total "Retained Acid," per 100 C.c., Molecular	Total Acetone Bodies, per 100 C.c., Molecular	Total Undetermined "Retained Acid," per 100 C.c., Molecular
April 14.....	1,160	650	510	0.0289	0.0100	0.0189

CASE 4.—P. B. B. K., a girl, aged 22, entered the hospital on April 14, 1923, in coma. Diabetes was of sixteen months' duration, and she had been receiving insulin at home for two months previous to entry. A week before entry she developed a sore throat and fever, with resultant decrease in tolerance and development of acidosis. Her physician continued the administration of insulin, and in addition advised forced fluids and a carbohydrate diet. Despite this treatment, acidosis persisted, and she became unconscious twelve hours before being sent to the hospital. She died two hours later, blood and urine analyses yielding the results given in Table 8.

As can be seen, there was a marked degree of acidosis with a large undetermined "retained acid" fraction in the blood, showing that the acetonemia was not accountable for the depletion of the alkali reserve which was present. The undetermined acid concentration of the urine was 510 c.c. to the liter, a figure much higher than our average normal. From this evidence we believe that the acidosis present was only in part due to acetone bodies and that other acids than the ketones were a factor in producing death.

Case 5.—P. B. B. H., a woman, aged 53, who entered the hospital on April 5, 1923, had diabetic symptoms of a year's duration. Three weeks before entry she became very weak and thirsty, and on the morning of admission suddenly had an epileptiform convulsion and became unconscious. She was brought to the hospital a few hours later.

The history was not typical of diabetic coma. However, physical examination gave no evidence of any cerebral lesion; lumbar puncture was normal; there were no signs of uremia, and the patient had acidosis, acetonemia, glycosuria, acetonuria and a blood sugar concentration at entry of 0.53 per cent. The observations given in Table 9 were made on acidosis.

The striking feature in this case was the marked degree of acidosis present in the first blood sample without a corresponding blood acetone body concentration, and the presence in the urine throughout of a large proportion of

Table 9.—*Acidosis in Case 5*

	Urine			Blood		
Date, 1923	Total Organic Acid, C.c. N/10 per Liter Urine	Total Acetone, C.c. N/10 per Liter Urine	Total Undetermined Acid, C.c. N/10 per Liter Urine	Total "Retained Acid," per 100 C.c., Molecular	Total Acetone Bodies, per 100 C.c., Molecular	Total Undetermined "Retained Acid," per 100 C.c., Molecular
April 5	790	250	540	0.0251	0.0090	0.0161
6	900	340	560	0.0150	0.0074	0.0085
7	1,000	510	520	0.0127	0.0067	0.0060
9	1,340	680	660	0.0108	0.0051	0.0057
13	840	430	410	0.0090	0.0051	0.0038
17	680	230	450	0.0086	0.0029	0.0057

unidentified organic acid. We believe therefore that in this case, also, other acids than the acetone bodies were in part responsible for the acidosis present. The patient was given insulin and sodium bicarbonate at entry with an almost immediate improvement. After consciousness was regained a few hours later, the subsequent course in the hospital was uneventful.

COMMENT

On the whole, the foregoing data suggest that in certain cases of diabetic acidosis other organic acids than the acetone bodies are encountered, and play a part in the production of symptoms. These acids may be excreted in the urine in larger concentration than found in normal urines. Under these conditions the fall of the plasma bicarbonate below 80 volumes per cent. is usually in excess of that accountable for by the concentration of acetone bodies in the blood.

These observations appear to be of both theoretical and practical significance. They are of theoretical significance as one naturally wonders what such organic acids may be and what part they play in the disturbed metabolism of diabetes. We have no information on this point.

These observations are of practical significance for two reasons: The parallelism between the excretion of total organic acids and of the acetone bodies is so striking in the vast majority of instances as to give a fair index of the acetone body excretion. The titration is simple and consumes little time. Therefore it may be used to advantage for routine work when more specific information in regard to the acetone body excretion is required than that afforded by the qualitative diacetic acid or acetone reaction but when highly accurate analyses are not needed. The only objection to the method which we have found is that urines containing large amounts of albumin will give high organic acid titration readings on account of their albumin conten. To the best of our knowledge, however, this source of error has not been present in the diabetic urines discussed in this paper. Moreover, a high degree of albuminuria is not often found in diabetic urines.

In the second place, the facts reported are of clinical significance as they suggest that patients with severe diabetic acidosis can be separated into at least two groups. The first group comprises those cases in which the acetone bodies alone appear responsible for the acidosis. In these cases, the unidentified organic acids excreted in the urine are not in excess of normal; the urinary acid excretion consists almost entirely of acetone bodies, and the fall below 80 volumes per cent. of the alkali reserve of the plasma corresponds to the molecular concentration of the acetone bodies in the blood. These cases respond satisfactorily to insulin and do not necessarily require alkali. As insulin forces the oxidation of glucose, it checks the formation of the acetone bodies in the body, the accumulation of acetone in the blood diminishes, the alkali reserve increases, the excretion of acetone bodies becomes less, and the clinical picture of acidosis disappears.

The second group comprises those cases in which other acids than the acetone bodies appear to be a factor in producing acidosis. In these cases, the concentration of unidentified organic acids excreted in the urine is in excess of normal, and the fall below 80 volumes per cent. of the alkali reserve of the plasma is much greater than can be accounted for by the molecular concentration of the acetone bodies in the blood. These cases appear to require alkali as urgently if not more urgently than they require insulin, since insulin will clear up the acetone body acidosis but may not affect the acidosis due to other acids, and the alkali released by the disappearance of acetone from the blood and tissues may be insufficient to clear up the condition completely.

Severe diabetic acidosis is always a condition of emergency, and the necessary analyses to separate the two types of cases described are time consuming. In the treatment of any given case of severe diabetic acidosis during the critical period, therefore, it seems reasonable to advise the use of insulin, forced fluids, liberal carbohydrate diet, and

small doses (from 15 to 25 gm. per day) of sodium bicarbonate as offering the most sensible and hopeful form of therapy. This plan of treatment has already been recently proposed by Campbell,[15] by Bock, Field and Adair, and by Foster.[16] The results reported by these workers are sufficiently striking to justify the conclusions drawn. Our results, obtained from a somewhat different point of view, offer confirmatory evidence pointing to what appears to be a rational treatment of severe diabetic acidosis.[17]

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15. Campbell, W. R.: Ketosis, Acidosis and Coma Treated by Insulin, J. Metabolic Res. **2**:605-635, 1923.

16. Foster, N. B.: Insulin in Diabetic Coma, Reported at the Meeting of the Association of American Physicians, May, 1923.

17. The insulin used in this study was insulin-Lilly.

THE SPECIFIC GRAVITY OF THE URINE*

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WITH COMMENTS† BY

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SAN FRANCISCO

In a recent number of the ARCHIVES OF INTERNAL MEDICINE[1] appeared a paper by T. Addis and Marjorie G. Foster under a title identical with the one given to this communication, wherein were offered experimental data which seemed to them to lead to the following conclusions:

> The specific gravity of the urine of normal persons was measured under varying conditions designed to place a strain on the concentrating activity of the kidney. It was found that not even an approximate idea of the work of the kidney in the excretions of solids could be obtained from the results. It is therefore concluded that specific gravity determinations cannot form part of any method intended to measure the amount of secreting tissue in the kidney.

Although it appeared to us evident that the data as presented had been wrongly interpreted, we appreciated the possibility of correct conclusions in spite of false premises and faulty logic. Consequently, we undertook to secure independent data and to analyze them after their procedure; we sought the aid of Dr. Addis in acquainting us with the detailed records of his experiments reported in summary form. He aided us cheerfully, and his cooperation is hereby gratefully acknowledged.

We deem it important to quote freely and in extenso from the paper of Addis and Foster, not only for clearly demonstrating the steps by which they arrived at their erroneous conclusions, but as well because we find occasion to offer criticism that has general applicability.

Addis and Foster "planned to determine whether there might not be certain special conditions under which the specific gravity of the urine could be used as a means for estimating the amount of secreting tissue in the kidney." They reasoned that "if the specific gravity really does give the concentration of solids in the urine it can be used in conjunction with a determination of the rate of urine excretion to measure the amount of solids excerted per unit of time. This is a measurement which might very well be related to the amount of secreting tissue in the kidney."

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1. Addis, T., and Foster, Marjorie C.: The Specific Gravity of the Urine, Arch. Int. Med. **30**:555 (Nov.) 1922.

Seeking to induce a demonstration of the maximal concentrating capacity of the kidney, a group of subjects who abstained from fluids for twenty-four hours were put on a constant diet low in fluids, protein and salts. Five experiments were performed on this group of subjects. In each of these, only the night twelve hour samples of urine were collected for analysis. In the first experiment nothing was fed the subjects at the beginning of this twelve hour period. In the other four experiments, specific substances were ingested by the subjects at the beginning of the night period as listed in Table 1. Each sample of urine had quantitative estimations of chlorin, phosphorous and urea in addition to measurements of its volume and specific gravity.

TABLE 1.—*Averages from Ten Normal Persons Under Five Different Conditions*

Conditions	Specific Gravity	Volume in C.c.
Fluid restriction only	1.027	242
Fluid restriction and addition of 30 gm. urea in 15 per cent. concentration	1.025	597
Fluid restriction and addition of 10 gm. sodium chlorid in 5 per cent. concentration	1.028	391
Fluid restriction and addition of 10 gm. sodium acid phosphate in 5 per cent. concentration	1.035	213
Fluid restriction and addition of 20 gm. urea, 5 gm. sodium chlorid and 5 gm. sodium acid phosphate given in 200 c.c. water	1.025	616

Reproduced from paper by Addis and Foster.

Continuing with a discussion of Table 1 the authors state:

Contrary to expectation these figures show that the specific gravity of the urine is not greater after the addition of urea, sodium chlorid or a mixture of urea, chloride and phosphate, than after fluid restriction alone. . . . But the main point of interest lies in the fact that the specific gravity results cannot be accounted for fully by the urine volume changes. Their inadequacy can be shown by a consideration of the amount of urea, chlorid and phosphate which were secreted. Thus, in the experiment with simple fluid restrictions the total amount of all three substances was 8.44 gm. $(NH_2)_2CO$, 5.40 gm.; + NACL 1.78 gm.; + NAH_2PO_4 1.26 gm.). When the mixture was taken the total amount eliminated was 30.19 gm. $(NH_2)_2CO$, 22.0 gm.; + NACL 4.63 gm.; + NaH_2PO_4 3.56 gm.). It would be conservative to assume that these three substances together made up more than 75 per cent. of the total solids of the urine and the remainder cannot have been far from constant since urines were from the same group of subjects on a fixed diet. The figures 8.44 and 30.19 may be used as an indication of the relative concentration of total solids in the two experiments. In the one case there is 8.44 gm. in 242 c.c., a 3.48 per cent. concentration of solids. In the other, there is 30.19 gm. in 616 c.c., a 4.90 per cent. concentration of solids. If the specific gravity of the urine depended only on the relation between the solids and the water in the urine we should expect to find a higher specific gravity in urine with 4.90 per cent. solids than in one with 3.48 per cent. solids. But the table shows that the reverse is true, for with 3.48 per cent. solids the specific gravity is 1.027 and with 4.90 per cent. the specific gravity is 1.025.

The foregoing reasoning is founded on an unwarranted assumption concerning the relationship of total solid weight to the weight of the

specific substances determined by Addis and Foster. It is quite improbable that when a constant diet is the source of a given amount of chlorin, phosphorous and urea, the ratio of the weight of these substances (calculated as sodium chlorid, sodium dihydrogen phosphate and urea) to the weight of the total solids is approximately the same as that obtained after the addition of sodium chlorid, sodium dihydrogen phosphate and urea to this fixed diet. While truly enough the weights of these substances in physiologic urine may represent at least 75 per cent. of the total solids as in the first experiment Table 1 (nothing added to diet), they represent at least 95 per cent. or more of the total solids in the fifth experiment Table 1 (added salts and urea). This

TABLE 2.—*Results in Experiments 1 and 5*

Name	Volume in C.c.	Specific Gravity	Urea, Mg. per C.c.	A* Sodium Chlorid, Mg. per C.c.	Sodium Dihydrogen Phosphate, Mg. per C.c.	Total Urea, Sodium Chlorid, Dihydrogen Phosphate, Mg. per C.c.	Coefficient †	Ratio ‡
(1) J.	205	1.032	35.1	4.68	6.04	45.82	0.143	3.29
(2) W.	330	1.015	14.7	4.85	3.80	23.35	0.156	1.71
(3) Mc.	138	1.029	25.9	11.60	6.05	43.55	0.150	1.47
(4) S.	286	1.029	26.0	10.64	5.67	42.31	0.149	1.50
(5) U.	255	1.025	19.0	11.9	5.95	36.85	0.148	1.07
(6) B.	168	1.036	25.7	8.56	8.45	42.71	0.119	1.51
(7) K.	165	1.034	35.6	8.63	7.50	51.73	0.133	2.21
(8) Sh.	393	1.014	14.05	2.85	2.95	19.85	0.142	2.42
				B§				
(1) J.	575	1.029	40.0	8.63	6.55	55.18	0.191	2.65
(2) W.	577	1.023	37.0	11.65	4.50	53.15	0.231	2.30
(3) Mc.	677	1.020	31.5	4.50	4.68	40.68	0.204	3.46
(4) S.	648	1.026	32.7	8.78	5.26	46.74	0.180	2.33
(5) U.	357	1.031	38.2	10.3	5.91	54.41	0.175	2.37
(6) B.	505	1.025	37.0	4.40	6.26	47.66	0.190	3.49
(7) K.	670	1.020	33.5	8.84	5.80	48.14	0.143	2.29
(8) Sl.	675	1.021	30.5	3.79	4.59	44.88	0.214	4.4
(9) Bo.	657	1.024	34.2	7.28	5.40	46.88	0.195	2.69

* Columns 1 through 5 contain the extensive data on which the summary of Experiment 1 (fluid restricted only), Table 1 is based. For convenience, we have expressed as milligrams per cubic centimeter the concentration of the specific compounds. In the original data percentile expressions were used. Columns 6, 7 and 8 are added by us as based on data in Columns 1 through 5.

† Column 6 divided by last three figures of the specific gravity.

‡ Column 3 divided by the sum of Columns 4 and 5.

§ Columns 1 through 5 contain the complete data on which the summary of Experiment 5 (added urea, sodium chlorid and phosphate), Table 1 is based.

is clearly brought out by the analysis of the figures in Column 7, Table 2. The coefficients given therein are secured by dividing the weight per cubic centimeter of the substances estimated by the last three figures of the specific gravity. For any given specific gravity the greater the weight of the solids, the greater numerically the coefficient. In Experiment 1, Table 1 (restricted fluids only), the average coefficient is 0.143. In Experiment 5, Table 1 (added salts and urea), the average coefficient is 0.191. Coefficients based on estimations of total solids have been between 0.23 and 0.26.[2] The coefficients supplied by urine samples of

2. Long, J. H. J.: Am. Chem. Soc. **25**:257 (March) 1903.

Experiment 5 more closely approach those derived from estimations of total solids. The ratio of the coefficients of the two experiments—1 and 5—give an approximate measure of the proportion of the total solid weight the specific substances determined by Addis and Foster represent in each of the experiments. Taking the coefficient of Experiment 5, Table 1 (added salts and urea), as unity, that of Experiment 1 is 0.75.

The authors continue, then, discussion of Table 1.

> The explanation of this apparent paradox lies in the fact—known ever since the first specific gravity was measured—that each dissolved substance has its own specific effect on the specific gravity of a solution. This fundamental fact is generally ignored in discussions on the specific gravity of the urine and either tacitly or openly, it is assumed that the specific gravity measures the total concentration of solids.
>
> Some rough determinations of the specific gravity of varying concentrations of urea, sodium chloride and sodium acid phosphate are given in the accompanying figure.

Then follows a graph depicting the fact that in pure solution sodium chlorid and sodium dihydrogen phosphate for a given concentration induce a considerably higher specific gravity than does urea. A 1 per cent. sodium chlorid solution has about the same specific gravity as a 2.5 per cent urea solution.

The assumption that the specific gravity measures the total concentration of solids is more thoroughly grounded in fact than the authors' assumption that it does not. They ignore the work of Trapp, Haeser, Naubauer and Long.[2] The authors are much concerned about total solids, but confine their knowledge of the total solids of specimens in their experiment to assumptions—assumptions which, as explained above, led to erroneous deductions.

Now follows Addis and Foster's explanation of the "apparent paradox."

> This graph shows how it came about that the specific gravity of the urine was lower after taking a mixture of urea, chlorid and phosphate than after simple water restriction, even though the total concentration of solids was greater. It was lower because a greater proportion of the total solids consisted of urea which has less effect in raising the specific gravity than chlorids or phosphates.

Within the range of temperatures at which the specific gravity of urine is usually taken, a 2.5 per cent. urea solution in water gives about the same specific gravity as a 1 per cent. solution of a mixture of sodium chlorid and sodium dihydrogen phosphate (within the limits of proportions of these two salts as found in urine). Therefore, if the ratio of the concentration of urea to sodium chlorid plus sodium dihydrogen phosphate in a sample of urine was greater than 2.5, the tendency ought to be toward a relatively lower specific gravity, if this

explanation of the paradox is correct. In Column 8, Table 2, are given these ratios for each sample of urine. We see at once that the explanation of the paradox is refuted by an apparently new paradox. That not only do samples (comparing urines of the same subject in both experiments) with relatively greater concentration of salts as against urea give lower specific gravities, but a lower specific gravity is secured in a specimen with a higher concentration of all three compounds.

Thus a sample of urine of subject J., Experiment 5 (Table 2 B) has a specific gravity of 1.029 as against 1.032 in Experiment 1 (Table 2 A), even though the concentration of urea and salts in the former is higher. In fact, five of the eight subjects of the experiments supply samples of urine in which the higher specific gravity is of a sample with the relatively greater concentration of urea.

Table 1 summarizes the data from eight to ten subjects by expressing each of the three functions concerned, that is, concentrations of salts and urea, volume and specific gravity as a simple arithmetical average of each function taken alone. This is not at all permissible. It in no way gives the data of the specimen the term "average" seeks to picture—the specific gravity, volume and weight of specific substances in a composite urine of the sample secreted by all subjects at the same hours following a constant diet. The only way we know of actually obtaining such data is by mixing the total volumes or a given aliquot of the urines of all the subjects, taking a specific gravity reading and estimating the weights of the substances concerned.

It is not our purpose to discuss here the statistical methods for determining relationships. We need only emphasize the fact that Table 1 is a false summary of Table 2, on the data of which Table 1 is based. Eight specimens are hardly enough for statistical treatment. More important than the expression of a central tendency as given by an "average" is the measure of the deviation from that tendency—variability. If measures of the variability of the "average" of the three functions studied were included in Table 1, the unreliability of the average would be seen at a glance.

To what absurdities poor statistical handling may lead is seen in the following taken from Table 1:

Specific gravity 1.027 of a "Urine" with { 2.23 % urea, 0.736% chlorid, 0.520% phosphate }

and a

Specific gravity 1.025 of a "Urine" with { 3.57 % urea, 0.751% chlorid, 0.578% phosphate }

While the salt concentration is practically identical in both "samples," the urine having 1.4 per cent. more urea has the lower specific

gravity. This would make it appear that one could add urea to urine and thereby depress the specific gravity. This cannot be done.

The explanation of the apparent paradox induced by Addis and Foster is quite apparent. Measuring a portion of the urinary solids in two experiments they wrongly assumed that those measures bore the same relationship to the total solids of the urines of their experiments, and therefore drew conclusions concerning total solids and specific gravity. The difficulty was further complicated by the improper use of the arithmetical average in summarizing their data.

The number of specimens secured were too few to prove anything; and in all events, the conditions of the experiment made it impossible to conclude anything concerning the total solids of the urine.

In Table 3 are given seventy-one records of urine from the same person. The patient was on a fairly constant diet throughout the period of observation. The samples represent two hour specimens passed during the day and from eight to twelve hour samples of the night. Collections of samples extended over a consecutive period of more than a week. The specific gravities were taken at room temperature. The determination of the specific gravities was made by the drop method, employing Dr. William G. Exton's [3] immiscible balance which offers a satisfactory and accurate procedure. The coefficients in the last column of the table were estimated to enable one to draw some conclusions concerning the adequacy of the method here used for studying the relationship of total solids to specific gravity in urine. The mean of the coefficients is 0.1356 with an average deviation of 0.0118, which is 8.7 per cent. of the mean. An analysis of the coefficients in Long's [2] records (fifty-two cases) of his study of total solids shows the average deviation to be only 4.1 per cent. of the mean. And where, seeking to study only the products of metabolism, he attempted to allow for the effects of the sodium chlorid, he found that the average deviation from the mean was greater.[4]

A study of the relationship between the specific gravity and the total solids in urine demands estimations of total solids and not merely of certain constituents of the urine. Although the correlation of specific gravity measures and total solid concentration is not perfect—not the most unimportant reason for this may be limitations in accuracy for the recording and determination of these measures—it is strongly positive. For clinical purposes the specific gravity may serve as an excellent measure of total solid concentration.

3. Exton, W. G.: Trans. Am. Urological Assn. **12**:83, 1920.
4. Long, J. H.: J. Am. Chem. Soc. **25**:871 (Aug.) 1903.

TABLE 3.—*Seventy-One Records of Urine from Same Person*

	Specific Gravity	Urea, Mg. per C.c.	Sodium Chlorid, Mg. per C.c.	Sodium Dihydrogen Phosphate, Mg. per C.c.	Total Urea, Sodium Chlorid and Sodium Dihydrogen Phosphate, Mg. per C.c.	Coefficient*
1	1.0065	4.22	3.2	0.22	7.64	0.117
2	1.010	4.80	5.2	0.11	10.20	0.102
3	1.0205	17.1	9.6	0.50	27.20	0.132
4	1.0195	15.3	9.6	1.51	26.41	0.135
5	1.0285	33.0	4.4	4.72	42.12	0.153
6†	1.020	16.5	7.2	2.11	25.81	0.129
7†	1.0225	18.8	9.5	2.31	30.61	0.136
8†	1.0205	18.7	8.7	2.15	29.55	0.144
9	1.0135	11.2	6.5	0.99	18.69	0.138
10	1.0125	8.83	6.4	0.55	15.78	0.126
11	1.0095	5.25	5.1	0.22	10.57	0.112
12	1.014	9.22	6.9	1.16	17.28	0.123
13	1.025	31.2	1.6	4.30	37.1	0.148
14	1.030	34.9	1.5	4.57	40.97	0.137
15	1.0295	30.4	3.8	4.27	38.47	0.145
16	1.017	14.9	7.0	1.47	23.37	0.138
17	1.012	7.5	6.2	0.163	13.86	0.115
18	1.0195	12.7	9.6	0.59	22.89	0.117
19	1.0205	13.1	9.6	0.69	23.39	0.114
20	1.0285	26.5	9.6	3.33	39.43	0.138
21	1.0305	28.3	9.0	4.23	41.53	0.136
22	1.030	27.4	9.6	3.41	40.41	0.135
23	1.0225	20.6	9.0	3.51	33.11	0.147
24	1.0305	27.1	8.9	4.84	40.84	0.134
25	1.0285	24.6	9.7	4.11	38.41	0.135
26	1.021	20.5	7.2	1.51	29.21	0.139
27	1.032	35.8	5.0	4.62	45.42	0.142
28	1.019	13.3	9.7	1.16	24.16	0.127
29	1.0125	9.7	5.6	0.38	15.68	0.125
30	1.012	7.5	7.9	0.19	15.59	0.130
31	1.020	15.8	9.6	1.63	27.03	0.135
32	1.0325	40.4	5.8	3.84	50.04	0.154
33	1.033	41.2	6.4	3.76	52.36	0.159
34	1.030	30.9	8.0	4.49	43.39	0.145
35	1.0335	39.5	8.0	4.18	51.68	0.154
36	1.026	21.7	9.6	1.28	32.58	0.125
37	1.018	14.0	9.4	0.81	24.21	0.134
38	1.023	19.0	9.8	1.12	29.92	0.130
39	1.0225	20.3	9.6	0.74	30.64	0.136
40	1.025	25.0	9.8	2.71	37.51	0.150
41	1.0315	35.2	9.4	4.34	48.94	0.156
42	1.033	40.5	7.4	4.68	52.58	0.159
43	1.032	38.2	6.2	4.57	48.97	0.153
44	1.026	23.9	9.8	2.13	35.83	0.138
45	1.0255	25.5	9.8	1.47	36.77	0.144
46	1.020	15.7	9.6	0.81	26.11	0.131
47	1.026	28.0	7.2	2.83	38.03	0.146
48	1.038	47.8	8.6	3.99	61.39	0.162
49	1.0305	30.0	7.5	4.07	41.57	0.136
50	1.0265	28.4	9.7	3.14	41.24	0.155
51	1.0265	27.1	9.8	2.85	39.75	0.150
52	1.0095	8.84	2.2	1.12	12.16	0.128
53	1.023	22.5	9.8	1.98	34.28	0.149
54	1.0095	6.93	5.6	0 70	13.23	0.140
55	1.0095	7.50	2.2	3.29	12.99	0.137
56	1.018	16.2	7.0	2.25	25.45	0.142
57	1.022	21.7	9.7	1.71	33.11	0.150
58	1.012	8.73	4.9	0.93	14.56	0.121
59	1.0125	9.12	4.5	0.97	14.59	0.116
60	1.0175	13.7	9.7	0.54	24.04	0.142
61	1.0165	14.7	6.8	1.70	23.2	0.140
62	1.018	14.3	9.6	0.81	24.71	0.137
63	1.009	4.5	4.4	0.66	9.56	0.106
64	1.020	16.5	9.6	2.36	28.46	0.142
65	1.0225	20.3	9.6	2.48	32.28	0.144
66	1.0095	5.98	4.2	0.58	10.76	0.113
67	1.013	9.75	3.4	1.12	14.27	0.110
68	1.0135	9.93	5.6	1.18	16.71	0.123
69	1.010	6.14	5.0	0.85	11.99	0.120
70	1.0125	9.98	4.4	1.16	15.54	0.125
71	1.009	6.93	2.8	0.66	10.39	0.115

* Secured by dividing Column 5 by the last three figures of the specific gravity.
† Twenty-four (24) hour specimen.

COMMENTS

By Dr. Thomas Addis

Dr. Sharlit and Dr. Lyle read more in the paper by Miss Foster and myself than is actually there. They apparently suppose that our data led us to conclude that the specific gravity of the urine can never be used to obtain even an approximate idea of the total solids of the urine. There is, of course, nothing in our experiments which has any bearing on Long's conclusion that the total solids may be estimated within a certain limit of error from the specific gravity under the particular conditions of his experiments. What we did conclude was that the total solids could not be even approximately measured from the specific gravity under the patricular conditions of our experiments, these conditions being as far removed as possible from those observed by Long.

The error in the estimation of total solids from the specific gravity varies directly with changes in the relative proportions of the various urinary constituents. In normal persons under ordinary dietetic conditions it has been shown that the changes in the relative proportions of urea, chlorids, phosphates and other substances in the urine are not so pronounced as to introduce a large error. But it surely requires no labored statistical proof to allow the conclusion to be drawn that the use of any such coefficient as Long's will not give even an approximate idea of the total solid content of the urine when the usual relation between the proportions of urinary constituents in the urine has been completely destroyed by increasing the proportion of either urea, chlorid or phosphate. Under such conditions, a statistical proof is superfluous because the conclusion is a deduction from the elementary fact that equal amounts of urea and sodium chlorid have the same effect on the total solid content but have a very diverse effect on the specific gravity. As Dr. Sharlit and Dr. Lyle, referring to our work, say, "the conditions of the experiment made it impossible to conclude anything concerning the total solids of the urine." That is exactly what our experiments were designed to show, that is, that there are conditions under which the specific gravity must necessarily give an entirely erroneous idea as to the total solid content.

If total solid estimations based on specific gravity measurements were to be used in cases of chronic nephritis, there would be uncertainty as to whether under these pathologic conditions there might not be changes in the relative proportions of the various urinary constituents which would lead to serious error. For this reason alone we felt justified in concluding that "specific gravity determinations cannot form part of any method intended to measure the amount of secreting tissue in the kidney." But even if it were found that the total solids could be fairly accurately determined from the specific

gravity, the results would be as useless for estimating the mass of functioning renal tissue as are determinations of nitrogen, chlorid, or any other urinary constituent. Only the ratio between the total urinary constituents in the blood and in the urine could be expected to measure the amount of renal tissue.* But when it is remembered what extreme variations in the relative concentrations of urea and of chlorid occur in the blood when most of the kidney substance has been destroyed by disease, it is clear that specific gravity determinations could not be used. The urea concentration may increase to ten, twenty, or thirty times its normal value, while the chlorid concentration shows no appreciable change or tends to fall.

It may very well be that Long's coefficient may have certain uses in clinical work, but under the special conditions of our experiments, and for the particular quantitative purposes we were discussing in our paper, it is quite clearly inapplicable.

COMPARISON OF CONSTANTS FOR THE DETERMINATION OF VITAL CAPACITY

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Since 1917 there has been a general revival of interest in the study of vital capacity, as first brought forth by Hutchinson,[1] of England, in 1846. This renewed interest is primarily due to the thorough work of Peabody and Wentworth,[2] of this country, and Dreyer,[3] of England. The literature on the subject since 1917 has become extensive, both from the clinical and investigative aspect, and has been chiefly concerned with the determination of what the normal capacity should be for a given person. Many methods have been advocated as being best suited for the determination of the standard capacity, and there are almost as many different formulas as authors on the subject. Hutchinson attempted to show that the standard vital capacity varied directly with the height of the person. More recently Peabody and Wentworth have studied the problem of vital capacity, and have classified persons into groups according to their height. Bohr [4] was the first to object to the establishment of the standard based on height alone, and later Dreyer in an extensive and careful study demonstrated that the standard vital capacity varied according to the body surface more closely than with any other body measurement. West [5] and others have confirmed these observations.

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1. Hutchinson, J.: Von der Kapazität der Lungen und von den Athmungs-Functionen mit Hinblick auf die Begründung einer genauen und leichten Methode Krankheiten der Lungen durch das Spirometer zu entdecken, Braunschweig, F. Vieweg und Sohn, 1849.

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443-467, 1917.

3. Dreyer, G.: The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body, New York, Paul B. Hoeber, 1921. Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **197**:227-234, 1919. Dreyer, G., and Burrell L. S. T.: The Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, Lancet **198**:1212-1216, 1920.

4. Bohr, C.: Die funktionellen Änderungen in der Mittellage und Vitalkapazität der Lungen, Deutsch. Arch. f. klin. Med. **88**:382-434, 1917.

5. West, H. F.: Clinical Studies on Respiration. A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306-316, 1920.

Because of the multiplicity of formulas and methods, it was thought that a comparison of the results obtained by using the various methods on the same group of subjects would be advantageous. It was hoped that such a comparison might lead to the selection of some one method that was accurate, and at the same time simple enough for general routine use. With this purpose in mind, 165 men and 166 women were selected for study from the preoperative surgical group of the Mayo Clinic. All patients suffering from pulmonary and cardiac conditions, or from inanition, were excluded. The diagnoses of the conditions of those selected include lipoma, hernia, and various conditions unassociated with asthenia or cachexia. Such a selection affords a varied, but generally uncomplicated, type of condition, and thus serves to determine the applicability of the various methods. These subjects were patients such as would ordinarily be encountered by the physician or surgeon in

TABLE 1.—*Physical Measurements in Male Subjects Used for Vital Capacity Tests*

	Cases	Age, Years	Height, Cm.	Weight, Kg.	Vital Capacity, C.c.	Surface Area, Sq. M.	Circumference of Chest, Cm.
Schuster (Oxford).....	969	.....	176.5	68.5	4,315	1.83	....
West (Harvard).....	85	.....	173.5	64.5	4,651	1.78	....
Hewlett and Jackson (Stanford) (Arch. Int. Med. **29**: 513, 1922).....	400	18 to 30	175.9	68.5	4,646	1.84	....
Hutchinson (England).....	1,285	.....	171.5	68.3	3,602	1.80	....
Dreyer (England).....	16	13 to 52	.....	....	4,140	....	86.6
Mayo Clinic.....	165	19 to 70	171.5	69.0	4,487	1.80	89.8

his practice. As every formula was applied to each person examined in the group, the methods were subjected to the same variations, and it is, therefore, possible to determine the value of each from a comparison of the results.

The patients examined came from all parts of the United States and Canada, from the Arctic circle to Texas, and from the Atlantic to the Pacific seaboard. The majority, however, came from the middle western states and western Canada. This is of interest because the results reported by various authors would seem to indicate a variation in the normal vital capacity for people from various countries, or even from different sections of the same country (Tables 1 and 2). Our figures can be considered as a fairly representative average of the whole country, although the number of determinations is too few to form a premise for conclusive argument.

Dreyer demonstrated that the vital capacity varied for training, sex, and certain occupations, a fact that is too often overlooked, and is left out of account in practically all other methods. In our series, many occupations are listed, and the ages vary from 14 to 70 years, therefore

comprising a fairly representative group. Familiarity with the procedure and the cooperation of the patient influence the results in measuring vital capacity, and must be considered before drawing conclusions as to what is the normal vital capacity of a given person. Pratt's observation is of great interest: "Furthermore, the vital capacity test of the same person may vary from time to time. I have recorded the amount of variation of the vital capacity in nine persons with apparently healthy hearts and lungs, over periods ranging from fourteen months to three years and four months. Although the seven men in the group were urged to make a maximal exertion at each test, and they apparently did so, the variation was considerable, ranging from 100 to 550 c.c. In the period covered by these tests there was no decrease that could be attributed to increasing age." In this regard, it is of interest to speculate on the possibilities of the influence of light, temperature, atmospheric pressure, water vapor, extraneous stimuli and food ingestion on vital capacity determinations, both from a physiologic

TABLE 2.—*Physical Measurements in Female Subjects Used for Vital Capacity Tests*

	Cases	Age, Years	Height, Cm.	Weight, Kg.	Vital Capacity, C.c.	Surface Area, Sq. M.	Circumference of Chest, Cm.
West (Harvard)	44	.....	.....	....	3,338	....	....
Myers	94	20 to 30	161.8	57.3	2,992	1.60	....
Peabody and Wentworth	...	.....	.....	....	3,050	....	....
Mayo Clinic	166	14 to 66	160.7	61.6	3,061	1.62	77.9

and a technical standpoint. Haldane,[6] Krogh,[7] Lindhard,[8] Hasselbalch [9] and others [10] have demonstrated the influence of these factors on the gaseous interchange in the lungs and external respiration. Vital capacity is nothing more than a part of this intricate mechanism.

The spirometer used in our work was of the wet type, and especially constructed for our use by Mr. Little of the Mayo Clinic (Fig. 1). By means of this instrument, it is possible to determine the amount of air expired within 8 c.c. It is so delicately balanced that the slightest inspiration on the part of the patient is observed on the scale. A spring cock valve at the opening into the tank permits closure of the intake, or outlet, of air at any point in the respiratory cycle. The mouth piece

6. Haldane, J. S.: Some Recent Advances in the Physiology of Respiration, Renal Secretion and Circulation, Brit. M. J. **1**:409-413, 1921.

7. Krogh, A., in Abderhalden, E.: Handbuch der biochemischen Arbeitsmethoden, Berlin, Urban and Schwarzenberg, 1915.

8. Lindhard, J.: The Seasonal Periodicity in Respiration, Skand. Arch. f. Physiol. **26**:221-314, 1912.

9. Hasselbalch, K. A., quoted by Haldane: Footnote 6.

10. Hoover, C. F.: The Respiratory Significance of Moisture in the Air Spaces of the Lungs, Med. Rec. **93**:1008, 1918.

of the instrument is of nickle, may be easily and rapidly sterilized, and is so constructed that it can be firmly held in the mouth without permitting leakage.

All readings were taken with the person in the standing position, with all clothing removed from the chest, except a cape in the case

Fig. 1.—Spirometer used in work reported.

of women. The subjects were instructed to take the deepest possible inspiration and expiration, keep the nose closed, expiring at a fairly uniform rate, and preventing any possible escape of air about the mouth piece. We did not use a nasal clip because patients frequently complained that it annoyed them. We believe we obtained better results from closure of the nares by thumb and finger pressure. Leakage

about the mouth piece was easily determined, as the nickle became fogged if air escaped from about it.

All physical measurements were made in the nude, and in accordance with the instructions of the various authors; in the case of women, allowance was made for a sheet and cape, although the tape was applied next to the skin. To obtain the greatest accuracy, readings should be taken at the same time of day, in a room that is of uniform temperature, and on patients who have been protected against fatigue. From three to five, and even more determinations were made in each instance, the highest being accepted. Several patients cooperated so poorly that their readings had to be discarded, and if there was any suspicion of questionable endeavor, this was likewise done. An interesting observation was made in the following instance: A group of six men were examined individually, and the readings noted. Then all six were admitted to the same room at the same time, and a contest instituted to see who could get the highest reading. All but one increased his previous readings by several hundred cubic centimeters.

In order to compare the physique of our subjects with that of subjects examined elsewhere, the various measurements were tabulated (Table 1).

The deviation of weight from normal is not included in the table, because our normals were established from the table used on Toledo scales, and we were unable to ascertain the standards used by other observers. The average deviation for our subjects was 7.5 per cent., while that given by other observers was from 7.3 to 8.8 per cent.

From Table 1 it may be seen that our averages compare favorably with those of others, although our group is not so highly selected as in the other series represented. Thirty-two of our subjects were somewhat overweight (average 5.6 per cent.), and 122 were below weight (average 8 per cent.). The latter, however, in many instances had higher vital capacity readings than their calculated normal.

In Table 2, similar observations on females are compared with those of Myers,[11] West, Peabody and Wentworth. Here again it may be seen that our unselected series compares favorably with Myer's selected series. With regard to variation in weight, it was found that forty subjects were overweight, averaging 8.5 per cent., and 104 were underweight, with a percentage variation of 10.8 per cent. Like the men, these women had higher capacities than their calculated normals.

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11. Myers, J. A.: A Study of the Vital Capacity and Physical Fitness of Nurses, with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual Physical Fitness, Journal-Lancet **41**:252-257, 1921.

CHART FOR BODY SURFACE DETERMINATIONS

WM. BOOTHBY. R.B. SANDIFORD.
SEPTEMBER 1920.

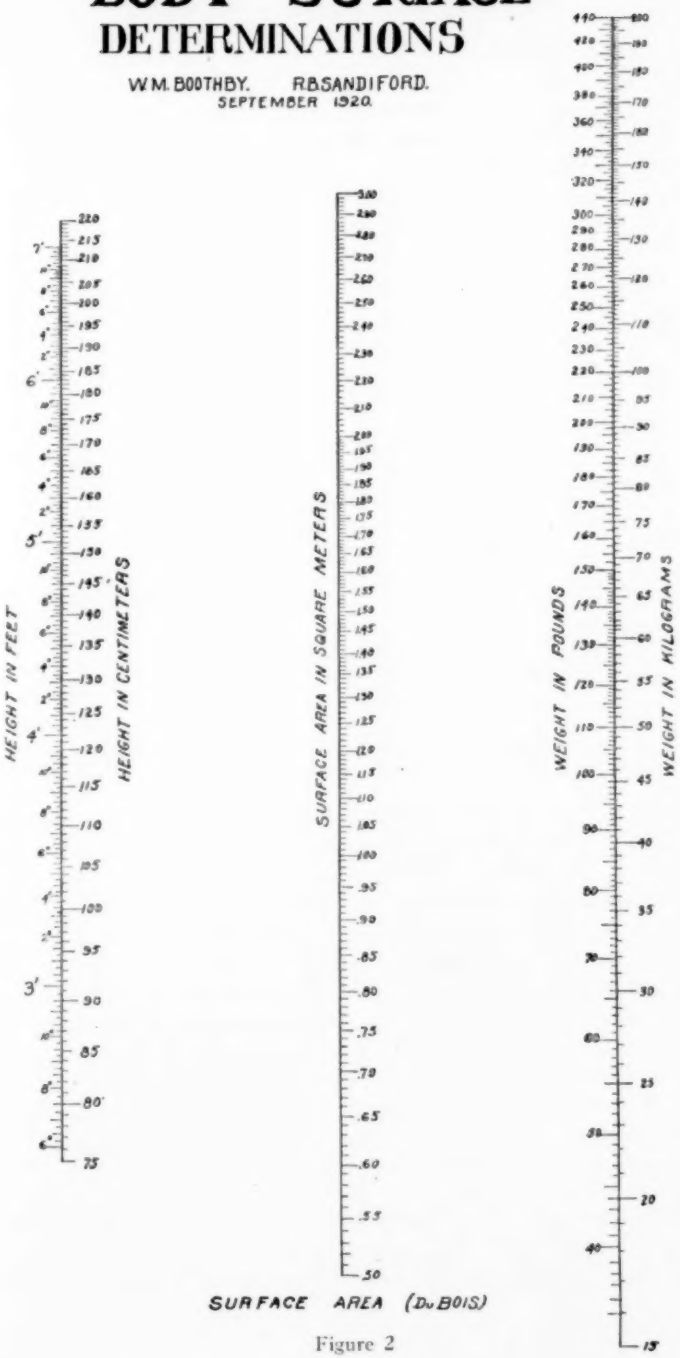

Figure 2

We were desirous of knowing whether the constants advocated by us when using the various formulas (seven in all) were approximately those of the authors themselves, or of other observers employing them. A comparison of the constants may be seen in Table 3. In Table 3, it will be seen that constant K1 in the male is practically identical with that obtained by Dreyer and by Schuster,[12] whereas it is greater than that of West. From Table 1 it will be noted that this may be in part accounted for by the larger vital capacity readings in West's series, while the weight averages are lower. This is in agreement with the findings of West himself, as he found that the K1 is 0.591 in case of athletes, in whom we have increased vital capacities without a proportional increase in the weight. The remainder of the constants, with the exception of that obtained by means of Lundsgaard and Van

TABLE 3.—*A Comparison of Our Constants with Those of Others Obtained by the Various Formulas*

	K 1	K 2	K 3	K 4	K 5	K 6	K 7
	W 0.72	W $\frac{2}{3}$	Ch 2	V. C.	V. C.	V. C.	100 × V.C.
	V. C.	V. C.	V. C.	W	H	B. S.	Chest Vol.
Observations on Men:							
Schuster	0.650	.....	1.82	.....	....	....	....
West	0.632	0.350	....	.....	26.5	2.61	63.0
Dreyer	0.690	0.457	1.84	.....	....	....	....
Peabody	.....	.....	....	.....	26.3	....	....
Lungsgaard and Van Slyke	.....	....	....	.....	....	....	45.0
Mayo Clinic	0.698	.....	1.88	0.007	26.1	2.49	41.4
Observations on Women:							
West	0.807	.....	....	.....	20.6	2.07	....
Myers	0.892	.....	....	.....	....	1.87	....
Mayo Clinic	0.936	.....	2.11	0.051	18.8	1.87	46.5

Slyke's [13] formula, are in fairly close agreement. In case of the latter formula, our findings force us to agree with West that when this constant is used, too large a percentage of the people have vital capacity estimations above normal. In the females, the variations are greater than in the males, but unfortunately, the amount of work carried out on females does not approximate that for males. In our series, 166 women were examined as against ninety-four in Myers', and forty-four in West's. The two constants that Myers has applied to his series, however, are in fairly close agreement with ours. The greater discrepancy in the female is due probably to the greater difficulty in taking body measurements, the unfamiliarity of the subjects with the technic of forceful expiration, lack of physical development and unwillingness to cooperate to the extreme of their ability.

12. Schuster, E.: First Results from the Oxford Anthropometric Laboratory, Biometrika **8**:40, 1911.

13. Lundsgaard, C., and Van Slyke, D.: Relation Between Thorax Size and Lung Volume in Normal Adults, J. Exper. Med. **27**:65-85, 1918.

We next tabulated the vital capacity readings according to the height divisions formulated by Peabody, and our results compare favorably with those obtained by him (Table 4). While the averages of the different series are fairly close, with the exception of the males in Group 1, there is much to be said against this method. As has been frequently pointed out, it discriminates against the person whose height comes on the borderline between two classes. This discrimination is especially important if one assumes that a variation of more than 10 per cent. below the calculated vital capacity is pathologic. In spite of this discrepancy, the general results compare fairly favorably with those of other methods, as will be seen later.

For comparative purposes, we next calculated the vital capacity of each subject, by each of the various formulas advocated, and the averages obtained are tabulated in Table 5, against the average of the

TABLE 4.—*Spirometer Readings*

	Height		
Men	Group 1 185.5 Cm. and Up Vital Capacity, C.c.	Group 2 173.3 to 182.5 Cm. Vital Capacity, C.c.	Group 3 159.5 to 173.5 Cm. Vital Capacity, C.c.
Peabody and Wentworth....	5,100	4,800	4,000
Mayo Clinic.....	5,450	4,885	4,305

	Height			
Women	Group 1 167 Cm. and Up, Vital Capacity, C.c.	Group 2 162 to 167 Cm., Vital Capacity, C.c.	Group 3 154.5 to 162 Cm., Vital Capacity, C.c.	Group 4 Below 154.5 Cm., Vital Capacity, C.c.
Peabody and Wentworth....	3,275	3,050	2,825	.....
Myers.....	3,260	2,970	2,973	2,857
Mayo Clinic.....	3,371	3,156	3,003	2,854

observed vital capacities for our subjects, as well as the average percentage variation of each from the average observed vital capacity.

In summarizing the tables, it is found that, in the case of males, the vital capacity calculated by means of West's formula (body surface in square meters times 2,500) gives the closest agreement with the observed vital capacity of any of the formulas, while the calculation on the basis of height and chest circumference, as well as class, according to Dreyer's method gives almost identical results. Dreyer originally, in creating his formula, used the stem length of the individual rather than the height; however, we used the height rather than the stem length because of the difficulty attached to measuring the stem length, especially in old persons.

In the case of females, West's formula (height in centimeters times 20) expressed the calculated vital capacity in the closest agreement with the observed vital capacity of any of the formulas. West's body surface formula (body surface times 2,000) comes next in order. Peabody and Wentworth's method for calculating the vital capacity

TABLE 5.—*Series of Cases Used as Basis of Comparison for Various Methods for Estimating Vital Capacity*

Formulas	Cases with Calculated Vital Capacity Higher than Observed	Average Vital Capacity Calculated Where It Was Higher than Observed, C.c.	Mean Difference Between Calculated and Observed Vital Capacity when Calculated Vital Capacity Was the Greater, C.c.	Average Calculated Vital Capacity Higher than Observed, per Cent.	Cases with Calculated Vital Capacity Lower than Observed	Average Vital Capacity Calculated Where It Was Lower than Observed, C.c.	Mean Difference Between Calculated and Observed Vital Capacity when Calculated Vital Capacity Was Lower than Observed, C.c.	Average Calculated Vital Capacity Lower than Observed, per Cent.	Grand Average Where Calculated Vital Capacity Varied from Observed, per Cent. for Each Person
				164 Males					
Body surface in sq. meters times 2.5 liters (West)	74	4,604	650	14.11	90	4,428	481	10.86	12.27
Height, cm. times 25 (West)	58	4,228	515	12.18	106	4,316	612	14.17	13.46
W 0.72 / 0.690 (Dreyer)	62	4,708	787	16.71	102	4,212	599	14.22	15.15
*Ch 2 / 1.82 (Dreyer)	64	5,015	1,108	22.09	99	4,225	629	14.67	17.58
*Vital capacity from weight (Dreyer's book)	48	4,532	697	15.38	115	4,126	651	15.77	15.65
*Height and circumference of chest (Dreyer)	64	4,424	526	11.88	96	4,368	549	12.56	12.28
*Standard of heights (Peabody and Wentworth)	65	4,363	523	11.98	97	4,352	575	13.21	12.71
21.2 times body weight plus 1,108 (Myers)	59	4,690	786	16.75	105	4,207	611	14.52	15.32
Weight in gm. times 0.006	72	5,057	974	19.26	92	4,147	656	15.81	17.32
				165 Females					
Body surface in sq. meters times 2 liters (West)	110	3,306	469	14.18	56	3,170	289	9.11	12.46
Height, cm. times 20 (West)	107	3,215	442	13.74	59	3,234	295	9.12	12.09
Standard of height (Peabody and Wentworth)	68	2,928	329	11.23	98	2,940	402	13.67	12.66
17.6 times body weight plus 900 (Myers)	105	3,474	600	17.27	61	2,969	365	12.29	15.43
W 0.73 / 0.690 (Dreyer)	124	3,635	725	19.94	42	3,093	334	10.79	17.62
Vital capacity from weight (Dreyer's book)	100	3,430	535	15.59	66	2,994	361	12.43	14.33
Height and circumference of chest (Dreyer)	103	3,370	521	15.46	48	3,117	302	9.68	13.62

* We are unable to obtain complete figures for 164 persons because the original authors' standards were not extensive enough to include all variations in height, chest circumference, and so forth

based on various height standards ranks third, for the smallest percentage variation from the observed vital capacity for both males and females.

From our series, it would, therefore, seem that West's formula (body surface in square meters times 2,500 in the case of men, and 2,000 in case of women) expresses the calculated vital capacity more accurately than any of the other methods, while West's formula (height in centimeters times 25 in case of men and times 20 in case of women) and Peabody and Wentworth's method are next in order. The Dreyer formula based on height and chest circumference is found to be less accurate for the female, owing to the difficulty in making chest measurements.

Objection may be raised to the use of body surface method of calculating vital capacity because of the difficulty in calculating the body surface. However, this difficulty is easily overcome by use of the chart constructed by Boothby and Sandiford for the determination of the surface area by the DuBois formula (Fig. 2). By means of this chart, all that is necessary is to connect the height and weight on the respective outside lines by means of a straight edge or rule, and read off the figures for body surface area where it bisects the middle line.

CONCLUSION

It seems to us that West's formula (body surface in square meters times a constant, 2,500 in case of men, and 2,000 in case of women) expresses the calculated vital capacity the most accurately and simply of any of the foregoing methods.

VITAL CAPACITY IN RELATION TO OPERATIVE RISK

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The question of operative risk is one of great interest as well as concern to the surgeon, and justly deserves his consideration. At the present time, he must estimate the operative risk from the patient's general condition, age, obesity and blood pressure, from the type of lesion and from his own skill and experience. While these factors may at times furnish the basis for an accurate estimation of the risk, they often involve danger to the less experienced surgeon, and at times even to the most skilled, on account of their variability and the difficulty of interpretation. Various conditions, such as nasal and bronchial infections, and the like, may lie dormant and give no indication of their presence until the patient's resistance has been lowered sufficiently by operation to permit exacerbation. It is often impossible to anticipate such complications even from the most careful history.

In view of the fairly accurate estimation which vital capacity gives of a person's physical fitness, it seemed plausible that operative risk might be estimated by the same method. We, therefore, took vital capacity determinations on 379 consecutive patients before operation, and checked the findings against the final outcome of the operation, as well as against the surgeon's own estimate of the operative risk, based on the patient's general condition. The risk for each patient was estimated on the basis of four, and the risk was calculated from the vital capacity determinations as follows:

TABLE 1.—*Risk Calculated from Vital Capacity Determinations*

Risk	Vital Capacity, per Cent.
1	—10 to normal
2	—20 to 10
3	—30 to 20
4	—30 and below

Of the 379 patients examined, twenty-three did not come to operation. The operative risk for the group of twenty-three, as calculated from the vital capacity determinations, was as follows: risk 1, fifteen; risk 2, four; risk 3, two, and risk 4, two. Two of the twenty-three

patients died while in the hospital under observation. For these patients, the operative risk as determined from the vital capacity determinations was 3 in one instance and 4 in the other; the surgeon in both instances estimated the risk at 4.

Nine (2.53 per cent.) of the 356 patients who came to operation died. The operative risks, as determined from the vital capacity findings for the nine fatal cases, are given in Table 2, and compared with the risk as estimated by the surgeon.

TABLE 2.—*Operative Risk in Nine Cases*

Degree of Operative Risk	Risk as Calculated from Vital Capacity, Cases	Operative Risk Calculated by Surgeon, Cases
1	3	2
2	3	5
3	2	1
4	1	1

Of the patients with an uneventful recovery, the risks as estimated from the vital capacity findings were as follows: risk 1, 233; risk 2, fifty-three; risk 3, thirty-six, and risk 4, twenty-five.

It was found that the surgeon considered the operative risk higher in seventy-two instances than the vital capacity determinations indicated, whereas the reverse was true in thirty-two instances. Several factors account for this variation. The operative risk calculated from the vital capacity was based simply on the patient's physical fitness. On the other hand, the surgeon had the benefit of his own knowledge of the type of disease and of his skill in performing the particular operation under consideration, and also of the internist's opinion regarding the patient's general condition. None of these factors was included in the calculation from the vital capacity readings.

For routine purposes, the determination of the operative risk from the surgeon's opinion is probably, on the whole, a more satisfactory estimate than that obtained by means of the vital capacity readings. However, if the surgeon does not have the benefit of experience, or the assistance of an experienced internist in making such an estimate, especially in questionable cardiac and pulmonary conditions, vital capacity determinations may be of the greatest aid. From whatever cause, the closer the approximation of vital capacity to tidal air, the graver will the risk become. When low readings are obtained, the surgeon would do well to institute preoperative measures, and to make further observations before attempting operation.

BASAL METABOLISM AND VITAL CAPACITY

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It is often observed that patients affected by exophthalmic goiter have a decreased vital capacity, and in taking the vital capacity of a number of such patients we noted that in several instances patients with the high basal metabolic rates had a relatively lower vital capacity than those with low metabolic rates. These observations prompted investigation to determine whether there is any fixed relationship between basal metabolism and vital capacity, and whether the thyroid secretion which causes the variations in metabolic rates likewise has an indirect compensatory action causing parallel fluctuations in the vital capacity. If this should be true, there would be at our disposal an easy method for determining thyroid activity.

With this purpose in mind, eighty-five subjects with goiter were examined. The diagnosis as to the type of goiter in each instance was based on the clinical findings, basal metabolic rates and postoperative histologic diagnosis in the majority of instances. The series was made up of twelve males and forty-six females with exophthalmic goiter, five males and twenty females with adenoma of the thyroid, two patients with thyroiditis, as well as with myxedema, and one with anorrhexia nervosa. Such a series was selected because of the wide range in basal metabolic rates it afforded.

The vital capacities were all taken with a wet type of spirometer, and a technic described by us in an earlier publication. In each instance the estimated normal vital capacity was calculated according to the following methods: (1) height in centimeters times 25 for males and times 20 for females (West [1]); (2) body surface in square meters times 2,500 for males and times 2,000 for females (West), and (3) from tables given in Dreyer's [2] "The Assessment of Physical Fitness." All three methods were used in order to obviate so far as possible

1. West, H. F.: Clinical Studies on Respiration. A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306-316 (March) 1920.

2. Dreyer, G.: The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the body, New York, Paul B. Hoeber, 1921.

errors that might occur through sudden changes in weight which so often occur in cases of exophthalmic goiter. The basal metabolic readings were all made in Dr. Boothby's laboratory at the Mayo Clinic, the open circuit type of gasometer being employed.

Repeated vital capacity and basal metabolic determinations were made on as many of the subjects as possible, in order to determine whether variations in the basal metabolic rate of the same person were accompanied by vital capacity changes. At first, similar determinations were made immediately following thyroidectomy, but these were discontinued on account of the poor cooperation of the patients because of their fear of causing a postoperative injury. In calculating the estimated normal vital capacity for the subjects, various factors, such as physical fitness, type of employment, training, age and sex were also taken into consideration.

TABLE 1.—*Observations on Relationship Between Basal Metabolic Rate and Vital Capacity in Fifty-Eight Patients with Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism*

Basal Metabolic Rate	Number of Cases	Vital Capacity Variation from Normal, as Calculated from West's Body Surface Formula, per Cent.
0 to + 20	1	—26
+20 to + 30	7	— 7.4 to —35.9
+30 to + 40	12	+ 0.2 to —39.2
+40 to + 50	14	+ 0.6 to —74.3
+50 to + 60	7	+18.2 to —44.8
+60 to + 70	9	— 8.6 to —32.6
+70 to + 80	3	+ 0.4 to —19.4
+80 to +102	5	—27.2 to —32.4

On tabulating the basal metabolic and vital capacity findings, it was found that although in the largest percentage of instances there was a tendency toward decreased vital capacity with increased metabolic rates, especially in cases of exophthalmic goiter, no definite relationship between the two was evident. A patient with a basal metabolic rate of + 17 per cent. may have just as great a decrease in vital capacity as one with a rate of + 70 per cent. (Table 1).

In a study of twenty-five patients with adenoma of the thyroid without hyperthyroidism, a similar inconstancy between basal metabolic rate and vital capacity was found to exist.

It was further noted that many of the patients with decreased vital capacity and increased metabolic rates had an increase of vital capacity and a decrease in basal metabolism after rest. That this was not dependent alone on the change in basal metabolic rate was evident from the fact that while, in most instances, the rate fell somewhat in those patients whose vital capacity increased on rest, it did not always fall. An increase in vital capacity can occur without lowering of the basal rate (Cases 7 and 14, Table 2), and a decrease in basal metabolic rate

on rest is not always associated with an increase in the vital capacity (Cases 3, 5 and 9, Table 2).

When the basal metabolic rate fell, an increase in vital capacity usually appeared but without any constancy. No rule could be applied to anticipate the changes that appeared.

It is true, however, on the whole, that the subjects with the greater decrease in vital capacity had an increase following rest, while less change was noted in those with smaller variations from normal.

It was found that the subjects with a decrease in vital capacity in most instances also had some cardiac decompensation, and that as the vital capacity decreased, the degree of cardiac decompensation became more marked. In almost every instance, it was found that it was the patients with the cardiac decompensation whose vital capacity

TABLE 2.—*Changes in Vital Capacity with Changes in Basal Metabolic Rate*

Case	Vital Capacity	Basal Metabolic Rate	Interval in Days Between Readings	Vital Capacity	Basal Metabolic Rate
1	2,302	+ 25	7	2,893	+ 7
2	2,667	+ 25	12	2,659	+ 40
3	2,832	+ 28	13	2,867	+ 14
4	3,102	+ 36	13	3,406	+ 23
5	3,632	+ 45	8	3,328	+ 30
6	2,066	+ 56	13	1,963	+ 47
7	1,998	+ 61	13	2,181	+ 62
8	1,859	+ 62	12	1,920	+ 53
9	2,615	+ 63	7	2,607	+ 47
10	3,356	+ 63	7	3,415	+ 45
11	2,259	+ 64	12	2,711	+ 33
12	2,589	+ 70	13	2,580	+ 78
13	2,242	+ 81	7	2,433	+ 66
14	2,328	+102	12	2,867	+108

increased with rest. Those who did not register an improvement in vital capacity had no decompensation, or being decompensated, gave no evidence of improvement. We, therefore, attempted to find the relationship that might exist between the degree of cardiac decompensation and vital capacity.

The patients were divided into five groups, according to the amount of decompensation, the first group being normal. As no definite measurable factor was available for estimating the decompensation, it had to be based on clinical manifestations, history and electrocardiograms. Dyspnea was of special value in making these calculations, as has been demonstrated by Peabody and Wentworth,[3] who found that a fairly reliable opinion as to the cardiac efficiency can be obtained from this symptom. The results obtained by this classification are given in Table 3.

3. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443-467 (Sept.) 1917.

It is seen from Table 3 that a relationship exists between cardiac compensation and vital capacity. Peabody and Wentworth, in 1907, divided a group of patients with cardiac disease into four groups on the basis of the vital capacity findings: those with a vital capacity of not more than — 10 per cent. of normal as Group 1; — 10 to — 30 per cent. as Group 2; — 30 to — 60 per cent. as Group 3, and below that as Group 4. In Group 1 there existed little or no cardiac decompensation and no dyspnea, while in each succeeding group these findings became more marked. In our series we classified the patients according to symptoms. Group 1 represented those having slight dyspnea and initial signs of cardiac inefficiency, while in each succeeding group the disability became more urgent. While differences exist between the two series, our findings tend to take the same course as those of Peabody and Wentworth.

TABLE 3.—*Relationship Between Cardiac Efficiency and Vital Capacity in Cases of Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism. (Cardiac Efficiency Classified on Basis of Scale of 4)*

Cardiac Efficiency	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
Normal	11	—16.7	—17.4	—13.6
—I	19	—15.4	—16.7	—16.7
—II	16	—24.4	—29.9	—26.9
—III	11	—32.6	—34.4	—35.6
—IV	1	—74.3	—67.8	—70.1
	Adenoma without Hyperthyroidism			
Normal	17	— 1.5	— 5.7	+ 1.8
—I	4	—11.7	— 7.9	— 7.4
—II	3	—28.6	—18.2	—23.4
—III	..	.....	.....	.....
—IV	1	—44.6	—41.0	—44.9

A division of the same series on the basis of edema alone likewise gave a similar indication of the deviation of the vital capacity from normal, as might be expected. The subjects were divided into groups on the basis of four, and the figures obtained are given in Table 4. As in the preceding classification, the basis of division is rather inaccurate, as it depends on individual interpretation of the classifying factor. From Table 4 it will be seen that in the higher grades of edema there was a diminution of the vital capacity, and that in a way the results are parallel to those obtained from the study of cardiac decompensation.

One is often impressed with the observation that persons vary in their response to thyroid secretion. In one person a moderate elevation in basal metabolism is accompanied by marked symptoms, while in another with the same, or even higher, rate only a few symptoms of hyperthyroidism exist. The vital capacity findings were therefore charted according to the severity of the symptoms to determine whether

this might show any relationship, but no constant relationship was found, although there was a tendency on the whole toward decreased vital capacity in those with the most marked symptoms (Table 5).

Exophthalmos and crisis likewise was of little value. In the former, no relationship between the degree of exophthalmos and vital capacity

TABLE 4.—*Relationship Between Degree of Edema (Extremities) and Vital Capacity in Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism (Edema Classified on the Scale of 4)*

Edema	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
0	28	−19.2	−23.3	−19.2
I	18	−20.5	−20.5	−21.3
II	10	−32.5	−36.1	−31.6
III	2	−37.2	−33.5	−38.7
Adenoma of Thyroid without Hyperthyroidism				
0	23	−11.5	−11.5	− 7.1
I	2	− 4.9	+ 1.2	+19.0

TABLE 5.—*Relationship Between Severity of Symptoms and Vital Capacity in Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism. (Severity of Symptoms Classified on Scale of 4)*

Severity of Symptoms	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
I	14	−17.5	−19.7	−18.9
II	23	−19.1	−24.1	−20.7
III	11	−27.2	−32.1	−32.8
IV	9	−33.5	−29.1	−22.6

TABLE 6.—*Relationship Between Duration of Symptoms and Vital Capacity in Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism*

Duration of Symptoms	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
½ year or less	15	−28.9	−32.0	−28.2
½ to 1 year	14	−19.4	−24.9	−17.2
1 to 1½ years	6	−14.1	−15.2	−18.1
1½ to 2 years	6	−17.1	−19.7	−16.7
2 to 3 years	2	−29.1	−27.6	−24.8
3 to 5 years	3	−18.0	−20.1	−14.6
5 to 10 years	4	−26.8	−29.1	−31.0

was anticipated, while in the latter we cannot say just what the relationship would be during the crisis, as the number of determinations has been too small, but between crises evidence of such a relationship is lacking. Family history likewise bears no relationship to the matter.

Due to the increased activity of the heart in hyperthyroidism, one might anticipate in time a gradual decrease in cardiac efficiency, provided

this increased activity along with any toxicity that may exist has an injurious effect on the heart. In order to determine whether such a condition existed, the vital capacity variations were grouped as to duration of symptoms into periods of six months each, and the results for exophthalmic goiter patients in our series are tabulated in Table 6.

While the number of determinations is really too small to permit the drawing of definite conclusions, it would seem that one cannot predict accurately the decrease in vital capacity that can be anticipated from the duration of the disease.

It was of interest to note that in all instances the women gave on the whole greater variations in the vital capacity findings than did the men. This is in agreement with the observations made in an earlier paper.

The findings on the two patients with thyroiditis examined followed the same general trend as those with exophthalmic goiter. In the patient with myxedema and the one with anorrhexia nervosa, each of whom had a decreased metabolic rate but a normal heart, the same relationship was found to exist. In fact, the anorrhexia nervosa patient, in spite of his loss of strength and weight, had an increased vital capacity.

As to the primary fundamental physicochemical cause of the decreased vital capacity in hyperthyroidism, we are still uncertain and must await further investigation. However, we believe the secondary and direct cause is the cardiac inefficiency which arises from the primary source, the thyroid.

FACTORS INFLUENCING VITAL CAPACITY

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Various considerations regarding vital capacity, as observed in a study of 225 men and 238 women at the Mayo Clinic, have already been presented. It became apparent that certain more general factors were repeated with such constancy that they must be considered in the interpretation of all estimations. Our observations regarding the relative importance of these factors are reported here.

SEX

It was anticipated that the vital capacity of the women of our series would be less than that of the men. We found in our group, which comprises the types of patients usually seen in ordinary practice, that the formula of West [1] was more suitable because of the ease of estimation and exactness. This formula takes into consideration the body surface measurements and a constant that varies with sex. Such constants as were proposed by West agreed with our findings, and we believe are best used when developing normals for comparison with actual spirometer readings. The factor of sex is not accidental or infrequently found, but seems to have a constant influence. West is not alone in making allowance for sex in estimating capacity. In our group, adults alone were studied, but a variation also obtains between boys and girls, as was shown by Stewart and Sheets,[2] who studied the vital capacities of 430 children. They found that boys always gave higher readings than girls. Menstruation may have some effect on the capacity of women, but we have no determinations to prove the supposition, and have found none in the literature.

Wittich, Myers, and Jennings,[3] however, have found that pregnancy has no influence on the readings, and cannot be a factor in its interpretation. Although their group is small, their conclusions are well supported. We did not make observations on pregnant patients.

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1. West, H. F.: Clinical Studies on Respiration. A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306-316 (March) 1920.

2. Stewart, C. A., and Sheets, O. B.: Vital Capacity of Lungs of Children, Am. J. Dis. Child. **24**:83-88 (July) 1922.

3. Wittich, F. W.; Myers, J. A., and Jennings, F. L.: A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, J. A. M. A. **75**:1249-1252 (Nov. 6) 1920.

PHYSICAL FITNESS

Physical fitness is so important a factor that we wish to recall particularly the work of Dreyer [4] in England, and of Hewlett and Jackson [5] in this country. Dreyer found it desirable to classify all people of the same stature into three groups on the basis of their physical fitness: (1) those active in athletics, military training, or vigorous outdoor labor were classified in Group 1; (2 and 3) those occupied in tasks less arduous or less conducive to physical development. He found that persons in Group 1 had higher vital capacity values than those in Group 2 or 3. This observation is important in estimating vital capacity, especially when readings become pathologic. We found that we could not disregard the individual fitness, for it became apparent that the readings for an athlete might be normal from the point of view of stature, and irrespective of training, but lower than normal for a man of his training. The reverse, however, is true of the person of poor physical training, who may have a vital capacity normal for himself, but so low as to be pathologic if compared with that of an athlete. The truth of these observations has been noted in all the selected groups studied, and has been particularly well demonstrated when young college athletes have been the subjects of observation.

AGE

Age, which plays such an important part in most bodily functions, does not seem to influence the vital capacity of adults to any marked degree before 50 or 60 years of age. Even after this period of life its effect is variable, and the decrease in vital capacity is generally found to run parallel with the change in general bodily turgor and elasticity, and to accompany the decrease in physical fitness which usually occurs at this period of life. In men in the seventies, the vital capacity readings may be normal, or even above normal. Unfortunately, the number of persons over 50 and 60 years of age studied are relatively few compared to the number studied before this period of life. In the table we have tabulated from the readings of 165 men and 165 women from our group the vital capacity for each decade and for each group on the basis of physical fitness. A small decrease in vital capacity is observed as the decades progress, but age plays an indefinite rôle. The degenerative changes which appear in man with advancing years, and the changes in height and weight provide many reasons for such a decrease, and are factors of such changing character and often so

4. Dreyer, G.: The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body, New York, Paul B. Hoeber, 1921; Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**:227-234, 1919.

5. Hewlett, A. W., and Jackson, U. R.: The Vital Capacity in a Group of College Students, Arch. Int. Med. **29**:513-526 (April) 1922.

difficult to determine that they are equally difficult to evaluate in making estimations. A rather marked difference appears in the groups arranged from the estimated physical fitness. Our findings agree with those of Dreyer, Peabody and Wentworth, and of Hutchinson [6] in a study of 1,775 subjects. Hutchinson found a definite decrease in vital capacity after 50 years of age. Pratt,[7] in a study of ninety cases, obtained results somewhat similar to those of Hutchinson, although there was apparently little variation in vital capacity until after 60 years of age. One factor which both Hutchinson and Pratt failed to take into consideration in classifying their results is physical fitness. This in part accounts for the apparently greater decrease in vital capacity after 50 years of age as compared with our series.

Relationship Between Age and Vital Capacity Classified on the Basis of Physical Fitness

	Male					
	Group 1		Group 2		Group 3	
Age, Years	Cases	Average Vital Capacity, C.c.	Cases	Average Vital Capacity, C.c.	Cases	Average Vital Capacity, C.c.
10-20	..	.....	1	3,910	..	.....
20-30	27	5,013	8	4,170	1	4,519
30-40	27	4,556	13	4,349	..	.....
40-50	22	4,827	24	4,294	1	2,685
50-60	17	4,765	10	3,813	..	.....
60-80	5	4,033	8	4,064	..	.....
			Female			
10-20	..	.....	2	1,993	..	.....
20-30	4	2,987	29	3,150	1	3,371
30-40	5	3,248	37	3,107	6	2,945
40-50	4	3,740	41	3,147	3	3,116
50-60	2	3,115	20	2,773	4	2,494
60-80	..	.....	5	2,697	2	1,851

BODILY MEASUREMENTS

Hutchinson, the first worker to undertake the study of vital capacity, noted that a relationship existed between vital capacity and various bodily measurements. He believed that it was probably a function of height rather than of any other measurement. Since that time it has been noted that a relationship exists between vital capacity and other bodily measurements, such as weight, stem length, chest circumference, chest capacity and body surface. Dreyer, in 1919, investigated the relationship between these various factors, with the exception of chest capacity, and came to the conclusion that vital capacity was more nearly a function of body surface than of any other bodily measurement. This was later corroborated by West, who also considered the relationship between chest volume and vital capacity. In an earlier paper on the

6. Hutchinson, J.: Von der Kapazität der Lungen und von den Athmungs-Functionen mit Hinblick auf die Begründung einer genauen und leichten Methode Krankheiten der Lungen durch das Spirometer zu entdecken, Braunschweig, F. Vieweg und Sohn, 1849.

7. Pratt, J. H.: Long Continued Observations on the Vital Capacity in Health and Heart Disease, Am. J. M. Sc. **164**:819-832, 1922.

subject, in which we reviewed the question of the relationship of vital capacity to various bodily measurements as sponsored by various authors, we likewise reached the conclusion that vital capacity is more nearly a function of body surface than of any other bodily measurement.

TEMPERATURE, PULSE AND RESPIRATION

We were interested in discovering whether variations in the fundamental bodily functions of temperature, pulse rate and blood pressure have an influence on vital capacity, or give any indication of its changes. We did not determine the exact influence of temperature on vital capacity because we could not study the effect of high temperatures on a sufficiently large number of persons. However, variations in temperature between 97 and 100 F., as studied in 463 persons without cardiac or pulmonary disease, did not appear to have any definite effect on vital capacity.

Blood pressure alone appears to have little effect on the vital capacity. In an analysis of this group of 463 subjects in which the systolic pressures varied from 80 to 220 mm. of mercury, little or no effect was found. The vital capacity varied neither directly nor inversely with the systolic, diastolic or pulse pressures. The pulse rate in persons without cardiac or pulmonary disease gave little indication of the vital capacity. However, if one accepts all cases without regard to physical ailments or deformities, it will be found that there is a tendency toward decreased vital capacity as the pulse rate becomes markedly increased. This is accounted for by the fact that in this group are included patients with exophthalmic goiter and cardiac and pulmonary diseases. A rapid pulse in a person without a complicating cardiac or pulmonary lesion does not indicate a decreased vital capacity, as shown in the chart.

DEFORMITIES OF THE THORAX

Deformities of the thorax deserve an important place in the consideration of vital capacity. Lundsgaard and Van Slyke [8] were the first to emphasize the relationship between chest volume and vital capacity. They believe that the relationship between the two was closer than between vital capacity and any other bodily measurement. However, Lundsgaard [9] has recently admitted the possibility of error in determining vital capacity as a percentage of chest volume from the three measurements of the chest, as advocated by Van Slyke and himself, in patients with deformities of the chest and embarrassed

8. Lundsgaard, C., and Van Slyke, D.: Relation Between Thorax Size and Lung Volume in Normal Adults, J. Exper. Med. **27**:65-85, 1918.

9. Lundsgaard, C.: Determination and Interpretation of Changes in Lung Volumes in Certain Heart Lesions, J. A. M. A. **80**:163-167 (Jan. 20) 1923.

respiration. Peabody and Wentworth [10] first called attention to the fact that flexibility of the thorax influenced the vital capacity. This is readily understood when one remembers that the thoracic cavity is enlarged by movement of the diaphragm and of the sternum and ribs upward, as well as the ribs laterally. The lungs can only fill with air to the extent which the thoracic cavity permits. In this connection one must consider ossification of the costovertebral joints, cartilage, etc., as possible influencing factors operating through a decrease of the flexibility of the thoracic frame. It was our good fortune to examine a man with ossification and fixation of the costovertebral joints, causing a complete immobilization of the thorax. The vital capacity was found

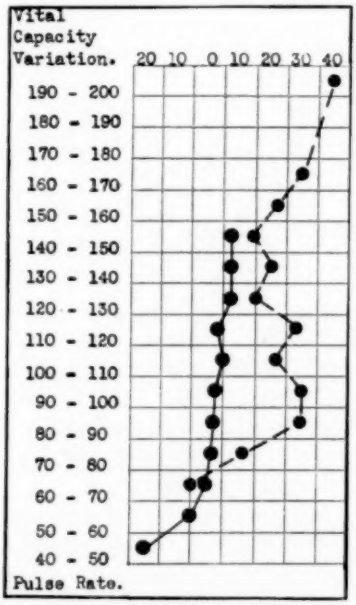

Chart 1.—Relationship between pulse rate and vital capacity in conditions with and without cardiac complications. The broken line indicates the pulse rate in conditions with cardiac complications (51); the solid line in conditions without cardiac complications (295).

10. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443-467 (Sept.) 1917. Peabody, F. W.; Wentworth, J. A., and Barker, Bertha: Clinical Studies on Respiration. The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, Arch. Int. Med. **20**:468-478 (Sept.) 1917. Peabody, F.: Clinical Studies on the Respiration. The Acidosis of Chronic Nephritis, Arch. Int. Med. **16**:955-966 (Dec.) 1915; Clinical Studies on the Respiration. The Effect of Carbon Dioxid in the Inspired Air on Patients with Cardiac Disease, ibid. **16**:846-864 (Nov.) 1915.

reduced as anticipated. The calculated vital capacity according to West's body surface formula was 4,800 c.c. while the observed vital capacity was 3,258 c.c., or 32.1 per cent. below normal. Strange to say, the patient was capable of participating in a game of ball or hockey without the least discomfort or dyspnea. Normal standards, estimated by any method, are subject to error in such persons, and ability to function without embarrassment is the best evidence of sufficient vital capacity.

MUSCULAR DEVELOPMENT

Peabody and Sturgis [11] found in cardiac cases that general muscular weakness and fatigue of the muscles of respiration are not important factors in causing a reduction of the vital capacity. In contradistinction to this conclusion, Levine and Wilson [12] conclude from a study of persons with irritable heart that fatigue results in the reduction of vital capacity. This conclusion they base chiefly on the observation that a greater decrease occurs after exercise than before, as compared with the results in normal persons. They found, however, that the small decrease in vital capacity in patients with irritable heart is not sufficient to account for the dyspnea that exists. It would seem to us that a weakening of the muscles of respiration could and should be a factor in causing a decrease in vital capacity. We often observe in conditions in which a portion of the respiratory musculature is incapacitated that decrease in vital capacity coexists, and that this decrease is proportionate to the importance and extent of the respiratory muscles involved. This was well demonstrated by a patient with chronic poliomyelitis who came under our observation. The intercostal muscles were paralyzed; the left side of the diaphragm was found to move only a little, and the right side about one half of its normal excursion, as observed under the fluoroscope. So far as we were able to determine, there existed no gross cardiac or pulmonary disease. This patient's vital capacity was found to be 1,510 c.c., or 65.4 per cent. of the normal as calculated from West's body surface formula. Although fatigue does not have as marked an effect on the respiratory muscles as was found in the foregoing example, it does have an effect. How great an effect we have been unable to determine.

ABDOMINAL PRESSURE

The effect of variations of intra-abdominal pressure on vital capacity is uncertain. It would seem probable that any condition in the abdomen that interfered with free movements of the diaphragm would influence it. However, in many such cases, pain, as well as

11. Peabody, F. W., and Sturgis, C. C.: Clinical Studies of the Respiration. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, Arch. Int. Med. **28**:501-510 (Nov.) 1921.

12. Levine, S. A., and Wilson, F. N.: Observations on the Vital Capacity of the Lungs in Cases of Irritable Heart, Heart **7**:53-61, 1918-1919.

complicating cardiac and pulmonary conditions, coexist, which make the results questionable. The observation of Wittich, Myers and Jennings that pregnancy influences vital capacity very little is of importance. Equally important is the observation of Lewis that abdominal pressure in animals under deep anesthesia plays no part in the production of respiratory curves. In our series, vital capacities taken on seven women suffering with large fibroids or cystic ovaries showed variations in vital capacity from + 9.2 per cent. to — 28 per cent. of the calculated normal; while in one man with a large abdominal tumor, due to a large hydronephrotic sac, the variation was — 13 per cent. of the calculated normal.

PLEURAL AND PULMONARY CHANGES

It is understood and easily demonstrated that anything which impinges on the pleural cavity and causes a decrease in lung volume from retraction or displacement of the lung tissue will also cause a decrease in vital capacity, depending on the amount of tissue affected, and the degree of interference with respiratory excursion or interference with the passage of air into other portions of the lungs. This reduction is found in cases of pleural effusion, pneumothorax, tumors of the chest wall, pleura and the mediastinum. Pleural adhesions which prevent the proper excursion of the lung must likewise be considered, as they cause a decrease in vital capacity, as demonstrated by Myers.[13] It is equally well known that anything which interferes with the admission or egress of air from the lungs will decrease vital capacity. The more marked the condition and the longer it interferes with the free passage of air, the more marked will be the reduction. Myers found in bronchial asthma, in which the free passage of air to and from the alveoli is impeded, that during the attack there is a decrease of as much as 18 to 20 per cent. in the vital capacity, which returns to normal after the attack, providing no complications exist or arise.

Dreyer and Burrell[14] and others have very well demonstrated the relationship that was found to exist between the extent of tuberculosis and the decrease in vital capacity, which is common in this disease.

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13. Myers, J. A.: Respiratory Organs in Health and Disease; Correlation of Symptoms, Vital Capacity Readings and Physical and X-Ray Findings in 619 Cases Examined for Pulmonary Tuberculosis, Am. Rev. Tuberc. **6**:702-706, 1922; Respiratory Organs in Health and Disease; Significance of Vital Capacity Test in Pulmonary Tuberculosis, Bronchial Asthma, Pneumonia, and Acute Infection Outside Respiratory Tract, Arch. Int. Med. **30**:648-667 (Nov.) 1922; A Study of Vital Capacity and Physical Fitness of Nurses, with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual's Physical Fitness, Journal-Lancet **41**:252-257, 1921.

14. Dreyer, G., and Burrell, L. S. T.: Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, Lancet **1**:1212-1216, 1920, **2**:374-376, 1922.

Siebeck [15] believes that this decrease in vital capacity in tuberculosis is due to an increase of the residual air volume, a decrease in the elasticity of the lung tissue and less forceful expiration. We have found that pneumonia, pleural effusions, bronchiectasis, emphysema, lung abscess, primary and secondary pulmonary growths and a large variety of less common diseases influence the vital capacity. The degree of reduction is an important prognostic consideration in all conditions when surgical intervention is indicated. The nearer the vital capacity approaches the tidal air, the graver will be the risk of operation.

CARDIAC CONDITIONS

Variations in cardiac efficiency are found to exercise a marked influence on vital capacity. Peabody and Wentworth, in 1918, in a thorough review of the question, demonstrated that, in cardiac conditions, the vital capacity varied with the cardiac efficiency. Opitz [16] further demonstrated that cardiac disease without decompensation does not influence vital capacity. These findings have been corroborated by other investigators dealing with the question. Our findings relative to the question of the relationship between cardiac efficiency and vital capacity have been reviewed previously, and will not be dealt with here. Cardiac condition should, however, be included in the list of known factors influencing the determination of the vital capacity.

HYPERTHYROIDISM

It is often noted that in hyperthyroidism, vital capacity is decreased. In a previous article, this entire problem was reviewed, and it was found that the vital capacity was proportional to the cardiac efficiency and bore no constant relationship to the degree of toxicity.

EXTRANEOUS INFLUENCES

There are various extraneous influences that must be considered in making vital capacity determinations. The question as to the most favorable position in which to place a person while making the determination must be considered, especially if one accepts the dictum that vital capacities 10 per cent. below the calculated normal are pathologic. A great deal of uncertainty still exists as to which position is best. Christie and Beams [17] found that the vital capacity taken in a reclining position averaged 5.5 per cent. below that taken in the sitting position.

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15. Siebeck, R.: Ueber die Beeinflussung der Atemmeckanik durch krankhafte Zustände des Respiration—und Kreislaufapparetes, Deutsch. Arch. f. klin. Med. **100**:204-220, 1910.

16. Opitz, R.: Vital Capacity of "Cardiacs," J. A. M. A. **78**:1686-1687 (June 3) 1922.

17. Christie, C., and Beams, A. J.: Estimation of Normal Vital Capacity, with Especial Reference to Effect of Posture, Arch. Int. Med. **30**:34-39 (July) 1922.

Rubow,[18] and also Hasselbalch[19] found that the vital capacity was greater in the standing than in the sitting position. All our readings were taken with patients standing, and we believe the essential point is that readings be always taken in the same attitude.

Peabody and Wentworth found little variation in vital capacities taken from day to day, while Pratt found that the vital capacity may vary considerably in normal persons over longer periods of time.

It is well to take vital capacities at the same time each day and under as nearly identical conditions as possible. Some patients permit psychic factors to influence them unduly. As we pointed out in a previous paper, patients are often capable of increasing their vital capacity under the stimulus of competition, so that whatever method is originally adopted should be adhered to. The time relationship to meals does not appear to have any influence on vital capacity.

There are undoubtedly various other factors that deserve consideration in vital capacity determinations. Among the more common factors that are generally disregarded are atmospheric pressure, temperature, water vapor, composition of the air, and light and darkness. That atmospheric pressure may have an influence on vital capacity is seen from the observation of Dreyer, who found that continued flying at high altitudes causes a decrease in vital capacity. It is a well-known fact that barometric pressure, temperature and water vapor exert a definite influence on air volume. In just what manner and degree these affect vital capacity is uncertain. Although atmospheric pressure may not influence determinations at any definite locality, when these are compared with similar readings taken in other localities, it may be of importance. Whether these factors account for the difference in the average vital capacity observed in groups of persons of the same training from different countries, is open to discussion. Lindhard,[20] in a study of the variations in respiration during various parts of the year in the Arctic circle, found that there was a difference in respiration in the light and dark periods of the year, and believed it was due to action of the light on the respiratory center, similar to the effect of temperature and barometric pressure on the respiratory center, but slower. He postulates that light has some influence on metabolism, therefore causing increased respiration. The purely physical influence of these factors on the air measured and the apparatus used should also be considered.

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18. Rubow, V.: Untersuchungen über die Atmung bei Herzkrankheiten. Ein Beitrag zum Studium der Pathologie des kleinen Kreislaufes, Deutsch. Arch. f. klin. Med. **92**:255-281, 1908.

19. Hasselbalch, K. A., quoted by Haldane, J. S.: Some Recent Advances in the Physiology of Respiration, Renal Secretion and Circulation, Brit. M. J. **1**: 409-413, 1921.

20. Lindhard, J.: The Seasonal Periodicity in Respiration, Skand. Arch. f. Physiol. **26**:221-314, 1912.

THE EFFECT OF DYSPNEA VARIOUSLY PRODUCED ON THE VITAL CAPACITY OF THE LUNGS

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MINNEAPOLIS

Dyspnea is one of the most constant findings in patients with heart disease. In these cases, Peabody and Wentworth [1] found that there is a diminution in the vital capacity of the lungs, and this diminution varies directly with the degree of dyspnea. These authors, however, attribute this diminution in vital capacity to mechanical factors, such as rigidity of the bony framework of the chest, ankylosis of the costal joints, diminution in the elasticity of the lung tissue, accumulation of fluids in the pleura, enlargement of the heart, enlargement of the liver, etc. These conditions, when present, undoubtedly cause a decrease in the vital capacity of the lungs. There are cases, however, in which such conditions are absent, but still the vital capacity of the lungs is decreased. Peters and Barr [2] report that the decrease in the vital capacity in heart disease does not depend primarily on anatomic factors, because of the absence of physical signs of congestion or fluid in the thorax, and because of the rapidity with which the vital capacity increases as compensation is established. They give no specific explanation, however, of the cause of this decrease in vital capacity of the lungs. Various types of experiments, therefore, were undertaken in order to find an explanation for this decrease in vital capacity when no mechanical factors are present.

As in the pathologic cases dyspnea and the decrease in vital capacity are usually found together, we felt that by producing dyspnea in persons who are normal and who have a normal vital capacity, we might arrive at some definite conclusion as to the relation of the two phenomena.

METHODS

The methods used in the production of dyspnea were: (1) rebreathing air, thereby increasing the carbon dioxid tension of the inspired air; (2) muscular effort such as running; (3) combination of running and rebreathing; (4) breathing air with reduced oxygen tension.

A Krogh [3] spirometer of 8 liter capacity was used in most of the experiments. A modification of the Hutchinson [4] spirometer was used

1. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.
2. Peters and Barr: Am. J. Physiol., December, 1920.
3. Krogh: Skand. Arch. f. Physiol. **27**:100, 1912.
4. Hutchinson: Med. Chir. Trans. **29**:137 (April 28) 1846.

for the study of oxygen diminution in the inspired air. It was found necessary to use rubber tubing with a wide lumen for our connections, because with narrow tubing the subject had to breathe against resistance, a factor which in itself decreases vital capacity. Soda lime was used to absorb the carbon dioxid produced by rebreathing, and thus the effects of anoxemia were studied. In all these experiments a closed circuit was formed between the patient and the apparatus. In order to assure a maximum inspiration, the subject was asked to inspire as deeply as possible, hold his breath for a moment, and make one or two attempts to inspire. Immediately afterwards, he was connected to the spirometer, expired as deeply as possible and finally made one or two further attempts to expire. This method assured a constant reading, especially when single readings were taken.

TABLE 1.—*Rebreathing at Tidal Air Amplitudes*

No. of Experiment	Total Length of Rebreathing in Sec.	Total Air in Circuit in C.c.	Average Vital Capacity in C.c.		Average Tidal Air in C.c.		Measured Minute Volume in Liters		Respiratory Rate per Minute		Fall in Vital Capacity in C.c.	Rise in Minute Volume in Liters	Difference Between Final Tidal Air and Vital Capacity, C.c.
			Beginning	End	Beginning	End	Beginning	End	Beginning	End			
1	122	8,360	5,160	4,160	1,312	3,520	21.16	55.96	14	16	1,000	34.80	640
2	109	7,880	5,080	3,976	1,550	3,992	24.80	119.76	16	30	1,104	94.96	—16
3	102	8,000	4,880	4,770	2,400	3,256	24.00	40.64	10	10	110	16.64	1,514
4	134	7,920	5,120	4,248	1,016	3,848	12.19	107.92	12	28	872	95.73	400
5	126	7,600	4,800	4,040	1,336	3,368	16.08	100.32	14	29	760	84.24	672
6	129	7,300	4,560	3,880	1,168	3,664	16.35	90.48	14	26	620	74.13	216
7	155	7,364	4,464	4,120	856	3,328	19.52	89.12	14	26	344	69.60	792
8	120	7,140	4,340	4,048	1,680	3,336	24.60	37.00	14	20	292	12.40	712
9	420	23,480	4,160	3,760	792	3,334	16.20	93.60	14	28	400	77.40	426
10	245	24,128	4,808	4,456	360	4,312	14.48	77.04	13	24	352	62.56	496
11	265	22,820	4,400	4,240	424	2,880	18.00	70.24	15	26	160	52.54	1,600
12	332	23,108	4,688	3,760	480	2,760	8.64	43.52	18	21	920	34.88	1,000
13	176	7,824	5,024	3,760	580	2,880	28.48	67.12	24	24	1,264	46.64	880
14	383	22,920	4,500	3,800	520	1,752	13.92	51.28	21	26	700	37.36	2,048
15	136	7,344	4,544	3,760	480	1,800	12.80	44.80	21	25	784	32.00	1,960
16	376	24,300	5,824	5,416	896	2,328	7.75	46.00	9	16	408	38.25	3,088
17	470	24,200	5,856	4,616	896	2,640	8.96	54.88	10	27	1,240	45.92	1,976
18	172	8,208	5,408	5,120	928	2,288	24.16	80.88	24	31	288	56.72	2,832
19	208	7,600	4,800	4,373	1,152	2,587	25.44	109.92	24	43	427	73.48	1,783

Two types of rebreathing were adopted: first, rebreathing with a tidal air amplitude; second, rebreathing with a vital capacity amplitude. When tidal air was used, the mind of the subject was occupied by reading or being spoken to. The tidal air and vital capacity immediately before the experiment were considered as the normals for that time. Rebreathing was continued until the subject could no longer hold out. In several experiments the rebreathing was continued to a point at which nausea and vomiting occurred.

When we speak of vital capacity, we must think of it in terms of the physiologic mechanism involved in exerting a given amount of voluntary effort, so that the maximum amount of air may be inspired or expired. This point of view has been taken into consideration in this work.

In the experiments in which rebreathing was carried out at tidal air amplitudes when marked dyspnea came on, from two to four vital capacity determinations were made. Other factors being equal, the total time of rebreathing depended on the amount of air present in the system at the beginning of the experiment. When the total air ranged between 7,100 and 8,300 c.c., the rebreathing interval was from 102 to 208 seconds, and when the air was from 23,000 c.c. to 25,000 c.c., the rebreathing interval was from 245 to 470 seconds. One, therefore, is justified in assuming that the total duration of rebreathing depends on the rate of change in composition of inspired air, namely, the increase

TABLE 2.—*Prolonged Breathing Against Resistance*
Vital Capacity Amplitudes

No. of Experiment	Total Length in Sec.	Respiratory Rate		Average Vital Capacity		Per Second Volume		Pulse Rate per Minute		Fall in Vital Capacity		Remarks
		Beginning	End	Beginning	End	Beginning	End	Beginning	End	Volume in C.c.	Per Cent.	
1	180	10	10	4,896	4,560	816	760	..	...	336	6.87	No dyspnea; sense of fatigue in respiration
2	330	9	10	4,595	3,856	689	642	80	102	739	16	No dyspnea; sense of fatigue in respiration
3	320	7	12	4,263	3,740	497	748	84	96	523	12.2	Apparent recovery from Experiment 2; no dyspnea; sense of fatigue in intercostal muscles

Prolonged Breathing at Vital Capacity Amplitude
No Resistance to Breath Against

Total Length in Seconds	Respiratory Rate per Minute		Average Vital Capactiy		Volume in Liters	Minute Volume	
	Beginning	End	Beginning	End			
2,732	9	4	4,576	4,496	41.36	18.16	Experiment was stopped at will; no dyspnea or fatigue at end of experiment

of carbon dioxid tension and decrease of oxygen tension. The point at which extreme dyspnea occurs and the subject is unable to continue rebreathing has been called by Peters and Barr [5] "the point of intolerance to CO_2." In these experiments, there was a definite but variable decrease in vital capacity. This decrease ranged from 2 to 25.1 per cent. of the normal. In general, it was found to be proportional to the degree of dyspnea. The degree of dyspnea was estimated partly on the subjective appearance of the subject and partly on the relative increase in minute volume. The analysis of the following experiments will serve to illustrate the method of making this estimation. In Experiment

5. Peters and Barr: Am. J. Physiol., December, 1920.

16 the subject rebreathed until he felt uncomfortable and thought that he could not keep up any longer. At this point he showed only moderate subjective dyspnea and objectively, in spite of the very high initial vital capacity, he had a rather low minute volume, comparatively slow respiratory rate and low tidal air. The result was that at the end of the experiment the final vital capacity was decreased to 5,416 c.c. When, however, the same subject was reassured that no ill effects would follow, he repeated the experiment and succeeded in rebreathing for 114 seconds longer. Even though the vital capacity in the beginning varied little, the final vital capacity in this experiment decreased to 4,616 c.c., a difference of 800 c.c.

TABLE 3.—*Rebreathing at Vital Capacity Amplitudes*

No. of Experiment	Total Length Rebreathing in Seconds	Total Air in Circuit in C.c	Respiratory Rate per Minute		Average Vital Capacity in C.c.		Measured Minute Volume in Liters		Fall in Vital Capacity, Volume in C.c.	Rise in Minute Volume in Liters
			Beginning	End	Beginning	End	Beginning	End		
1	100	7,838	8	13	5,068	4,715	40.30	61.30	323	21.00
2	110	7,647	11	19	4,847	3,912	53.32	74.32	935	21.00
3	105	7,666	9	18	4,866	4,424	43.80	79.64	442	35.84
4	120	7,500	8	20	5,000	4,180	40.00	83.60	820	43.60
5	98	7,836	11	19	5,096	4,398	56.40	83.56	698	28.16
6	130	7,390	8	12	4,590	3,310	36.72	39.72	1,280	3.00
7	126	7,180	9	12	4,380	3,847	35.04	46.16	533	11.12
8	206	25,900	8	11	5,000	4,069	40.00	44.76	931	4.76
9	128	8,023	7	13	5,223	4,554	36.56	59.20	669	12.64
10	100	8,147	6	8	5,347	4,550	32.08	36.48	797	4.40
11	110	8,160	6	12	5,360	4,072	32.16	48.88	1,288	16.72
12	124	8,093	6	17	5,293	3,972	31.76	67.52	1,321	35.76
13	103	8,040	5	13	5,240	3,649	26.08	47.44	1,591	21.36
14	112	7,840	6	15	5,040	3,232	30.24	48.48	1,808	18.24

Although the rate of respiration is an important factor to be considered, it appears that the decrease in vital capacity in this series is more closely related to the increase in the tidal air amplitude than the rate of respiration. In general, the greater the increase in final tidal air, the greater is the decrease in vital capacity. One may consider the difference between the final tidal air and the final vital capacity as the ultimate voluntary reserve of increase in amplitude of respiration. It is, perhaps, possible to estimate the degree of dyspnea from this difference. Thus, in Experiment 16, in which the dyspnea was only moderate, the difference between the final tidal air and vital capacity is 3,088 c.c. On the other hand, in the next experiment, in which the dyspnea was quite marked, this figure dropped to 1,976 c.c. In this experiment, even though the vital capacity was decreased by 1,240 c.c., and his final tidal air was 2,640 c.c., when these figures are compared with those in the sixth experiment, it will be noticed that in the latter, in spite of the relatively small decrease in vital capacity (620 c.c.) the difference between the final vital capacity and tidal air is as low as 216 c.c. That this person was subjected to an extreme dyspnea is also borne out by

the very high minute volume at the end of the experiment, namely 90.48 liters. One is, therefore, justified in concluding from these data that the subject in Experiment 17 had a great deal more reserve and could possibly keep up longer, whereas the subject in Experiment 6 was using his last resources to compensate for the dyspnea.

As the vital capacity determinations depend primarily on voluntary effort, there is a possibility that anticipation of results might produce a decrease in vital capacity. A number of experiments, therefore, were performed on subjects who did not know beforehand what the results would be, and who were willing to cooperate fully with us. These subjects were free from any apparent cardiac or pulmonary disease. The results in these subjects did not differ in any way from those obtained when the experiments were performed on ourselves.

A few experiments were performed with the subject breathing atmospheric air at vital capacity amplitudes, but against resistance. In spite of the absence of any subjective or objective dyspnea, there was a decrease in the vital capacity from 336 c.c. (6.87 per cent.) to 739 c.c. (16 per cent.). This decrease was undoubtedly the result of fatigue of the muscles of respiration caused by undue effort. Subjectively, voluntary control of these muscles was diminished, and the experiment was terminated on account of discomfort and the cramping of these muscles. That the decrease in vital capacity was not due to breathing per se at vital capacity amplitudes, is evident by the following experiment. Prolonged breathing was carried out at vital capacity amplitudes, and the resistance against breathing was minimized by the use of tubing with a diameter of 22 mm. It was possible to continue the experiment for forty-five and one-half minutes and then stop it at will. The vital capacity ranged within normal variations throughout the experiment. As one would expect, the respiration rate and the minute volume were decreased markedly. No dyspnea or fatigue were experienced subjectively.

In all the experiments in which rebreathing was carried out at vital capacity amplitudes, it was evident that the latter began to diminish gradually from the beginning, slowly at first and then more and more rapidly. The decrease in vital capacity at the end of the experiments ranged between 6.4 per cent. and 35.8 per cent. of the normal. In this series also, the amount of decrease in vital capacity depends on the degree of dyspnea at the end of the experiment. As the point of intolerance to carbon dioxid approaches, the extent to which rebreathing is continued has a marked effect on the degree and rate of decrease on the vital capacity. If, under such conditions, rebreathing is carried out a few seconds longer, the vital capacity is reduced markedly. The rate of

TABLE 4.—*Running Until Hyperpnea Followed by Rebreathing in Untrained Athletes*

No. of Experiment	Total Length of Rebreathing in Sec.	Total Air in Circuit in C.c.	Respiratory Rate per Minute		Vital Capacity in C.c.		Tidal Air in C.c.		Measured Minute Volume in Liters		Fall in Vital Capacity, Volume in C.c.	Rise in Minute Volume in Liters	Remarks
			Beginning	End	Beginning	End	Beginning	End	Beginning	End			
1 A	. .	.....	19	34	4,780	3,936	672	1,820	12.768	62.40	844	49.63	Lifted weight and ran until dyspneic; recovery from increased ventilation
7 B	...	.....	19	27.1	4,780	4,346	672	2,263	12.768	67.86	434	55.09	Exercise repeated until dyspneic
1 C	..	.....	19	23.3	4,780	4,240	672	2,240	12.768	87.11	540	74.34	No hyperpnea; apparent recovery from 1 B; exercise (running and lifting weights) continued until dyspnea
2 A	...	.....	19	30	5,166	4,293	857	2,980	16.36	89.40	873	73.04	Dyspnea by running down and up stairs of five floors
2 B	...	.....	19	38	5,166	4,160	857	2,549	16.36	97.32	1,006	80.96	Continued to run in room after recovery from increased ventilation until dyspneic
3 A	...	.....	19	36	4,600	4,300	480	2,915	9.12	104.94	300	95.82	Experiment done 6 hours after complete recovery from previous experiment; ran down and up stairs of five floors
3 B	...	.... .	19	27	4,600	4,300	480	3,120	9.12	91.68	300	82.56	Recovery from hyperpnea; ran in room until again dyspnea resulted
3 C	40	7,160	27	30	4,300	3,600	3,120	3,424	91.68	95.28	700	3.60	Rebreathing immediately after 3 B at tidal air amplitudes; vital capacity at beginning 240 c.c. (5%) less than at "A"
3 D	123	22,893	23	26	4,453	4,080	1,424	3,264	54.80	83.62	373	28.82	Rebreathing after recovery from 3 C
4 A	...	.....	20.8	27	5,140	4,773	1,747	2,944	36.276	83.04	367	46.764	Ran down and up stairs of five floors; dyspneic
5 A	...	.....	22.5	29	5,333	4,800	894	1,184	20.10	44.00	473	23.90	Immediately after 4; lifting weights until very tired but not dyspneic; unable to go on account of fatigue
5 B	111	33,280	29	32	4,800	4,800	1,184	2,032	44.00	65.024	60	21.03	Rebreathing immediately after 5 A; no extreme dyspnea, but sense of fatigue and no desire to continue
6 A	...	.....	20	28	4,740	4,613	784	3,152	15.68	86.98	127	70.30	Ran down and up stairs five floors; dyspneic
6 B	58	7,113	28	28	4,613	4,106	3,152	4,496	92.00	102.64	507	10.64	Rebreathing immediately after 6 A
7 A	...	.....	16	36	3,389	2,846	858	2,007	13.37	132.25	543	118.52	Ran down and up stairs; dyspneic
7 B	58	.....	36	36	2,846	2,253	2,007	2,253	132.25	81.11	593	Fall	Rebreathing immediately after 7 A; final vital capacity and tidal air are same

TABLE 5.—*Carbon Dioxid Absorbed. Rebreathing at Tidal Air Amplitudes*

No. of Experiment	Total Length of Rebreathing in Sec.	Total Air in Circuit in C.c.	Average Vital Capacity in C.c.		Average Tidal Air in C.c.		Minute Volume in Liters		Respiratory Rate per Minute		Fall in Vital Capacity, Volume in C.c.	Rise in Minute Volume in Liters	Remarks
			Beginning	End	Beginning	End	Beginning	End	Beginning	End			
1	245	8,824	4,129	4,129	1,315	2,003	19.73	33.49	15	16	0	13.76	No dyspnea; fulness of head, faintness, weakness, poor voluntary control; stopped on account of discomfort
2	268	7,840	3,973	3,746	1,029	1,773	19.90	55.24	11	33	227	35.34	Dyspnea; no nervous symptoms
3	258	7,867	4,302	4,000	574	2,285	8.05	41.15	14	18	332	33.10	No dyspnea; pulsating headache, sense of compression in head, weakness, poor voluntary control
4	295	8,702	3,144	2,289	1,061	1,073	15.92	22.53	15	21	855	6.61	Dyspnea; no discomfort or dulling
5	117	4,797	4,589	4,086	1,185	1,491	21.34	28.85	18	18	503	7.51	No dyspnea; symptoms as in Experiments 1 and 3
6	159	4,917	3,337	2,106	1,040	1,601	18.72	48.04	18	30	1,231	29.32	Dyspnea, cyanosis, some mental dulness, no headache or weakness
7	408	8,258	3,516	2,170	787	1,049	14.17	26.23	18	25	1,346	12.06	Pale, waxy appearance of face; lethargic, eyes half closed; loss of voluntary control
8	243	7,840	4,530	4,134	530	1,005	8.54	24.08	16	15	396	15.54	No dyspnea; symptoms same as in Experiments 1 and 3
9	271	5,454	3,179	2,086	604	1,515	9.66	28.79	16	19	1,093	19.13	Dyspnea; some unsteadiness, no cyanosis; no mental symptoms

respiration in this series was quite slow and increased only slightly until the onset of dyspnea. The relative increase in the rate of respiration in both series was approximately the same.

Two types of observations were made in the study of the relation of exercise to vital capacity, and rebreathing immediately after exercise or as soon as the apparent dyspnea disappeared. One set of experiments was performed on athletes at a gymnasium. It was found that ordinary floor exercise did not produce any increased ventilation of the lungs, and therefore did not appreciably change the vital capacity. Running was, therefore, adopted as the exercise of choice for the production of dyspnea. The final determinations were made at the point at which the subject was dyspneic. The apparatus was near at hand so that only a small interval of time elapsed between the end of exercise and the determinations. Nevertheless, some of the athletes so promptly recovered from dyspnea that little or no change in the final vital capacity occurred.

It seemed that prompt recovery in these subjects was due to the fact that they were athletes. Therefore, another set of experiments was carried out on untrained subjects. In most of these subjects the vital capacity was decreased after exercise. The tidal air and minute volumes were increased. Soon after exercise, in spite of the apparent absence of subjective dyspnea the tidal air was somewhat higher than normal, and the vital capacity remained below normal. If rebreathing was carried out at this stage, the interval was diminished by over one half of the rebreathing interval with the same amount of reserve air before exercise. Rebreathing in this series did not change the rate of respiration very much but increased the tidal air considerably. When the minute volume became quite high, it remained close to that level, so that at the beginning of rebreathing it was within the limits of dyspnea. After rebreathing, however, in most cases it rose higher than at the end of exercise.

Rebreathing after exercise is probably analogous to the conditions present in patients with heart disease. These patients, like our normal subjects after exercise, have a vital capacity lower than normal, and can hold their breath for a few seconds after a deep inspiration or a deep expiration, but less than normal. They both have a tendency to dyspnea and a shortened rebreathing interval. In the absence, therefore, of thoracic exudates or transudates or other mechanical conditions to cause an actual diminution in the capacity of the lungs, one is justified to assume that a decrease of the vital capacity of the lungs depends to a great extent on the degree of dyspnea.

The last series of experiments was carried out to determine whether dyspnea produced by conditions other than increase or inspired carbon

dioxid or exercise had the same effect on the vital capacity. In the cases in which there was a decrease in vital capacity, there was subjective dyspnea and objectively an increase in the minute volume. On the other hand, one is not certain of the results in those cases in which the mental symptoms were marked. Thus, in Experiment 7, toward the end the subject was lethargic and practically without any voluntary control over his respirations. In this experiment, therefore, it is difficult to decide whether the decrease in vital capacity is really due to an increased pulmonary ventilation or to a loss of control of his accessory muscles of respiration. In some of the experiments, the discomfort during the experiment was so great that the experiment was terminated before the onset of dyspnea. All attempts in the case of one subject to produce dyspnea were unsuccessful because of the severe sense of compression in the head, and the feeling of having received a blow on the head. The symptoms during this period, and for several hours afterward, were no different than those so well described by J. Barcroft[6] under the title "Acute Anoxaemia." When one compares the smooth and easy way of producing dyspnea by means of increased inspired carbon dioxid with the discomforting and probably dangerous method with oxygen want, one is justified in discarding the latter method, especially since the changes in the vital capacity cannot be well controlled with the latter method. Moreover, this method was recently tried from the same point of view as in our experiments and was found unsatisfactory by Stengel, Wolferth and Jonas.[7]

SUMMARY

1. Dyspnea was produced by the use of exercise, increased carbon dioxid tension in the inspired air and oxygen want.

2. When the pulmonary ventilation was increased, there was a decrease in the vital capacity.

3. The use of oxygen want for the production of dyspnea does not give well controlled results with reference to the study of vital capacity.

4. In a few experiments exercise produced a slight but noticeable increase in vital capacity.

5. After exercise, a condition is produced in the body that is quite analogous to that in patients with heart disease with reference to their vital capacity, the tendency to dyspnea and the shortened rebreathing interval.

6. The decrease in vital capacity of the lungs is secondary to dyspnea and depends primarily on conditions which produce dyspnea.

6. Barcroft, J.: Acute Anoxaemia, Lancet, September 4, 1920.
7. Stengel, Wolferth and Jonas: Trans. Assn. Am. Physicians, 1920.

7. Dyspnea, as experimentally produced, always was marked before any appreciable reduction of vital capacity was obtained. It is possible in patients who are physically incapacitated by disease that dyspnea may have a much more marked effect on the vital capacity of the lungs.

8. The reduced vital capacity, in part at least, is presumably due to the dyspnea which enters into the make-up of the clinical picture in patients with cardiac disease.

BOOK REVIEWS

NON-SURGICAL DRAINAGE OF THE GALL TRACT. By B. B. Vincent Lyon, A.B., M.D., Chief of Clinic, Gastro-Intestinal Department of the Jefferson Medical College; Attending Physician (formerly pathologist) to the Methodist Episcopal Hospital, Philadelphia. Cloth. Price $10.00. Pp. 640, with 175 engravings and 10 colored plates. Philadelphia: Lea and Febiger, 1923.

This volume presents in a detailed manner the author's extensive investigation of the diagnostic and therapeutic value of the nonsurgical drainage of the gall tract. Following an excellent chapter on the anatomy of the biliary system, the author devotes sections to a discussion of the fundamental principles on which the method is based; namely, the theoretical "law of contrary innervation" of S. J. Meltzer, and to a critical review of experimental work tending to cast doubt on the soundness of this underlying principle.

The technic of medical drainage of the gall tract is given in detail as well as the author's indications for its use in various pathologic and functional conditions. Numerous case protocols are appended to illustrate the employment of the procedure in the diagnosis and treatment of gall tract disease and other conditions in which its use depends on less well defined indications. Several of these protocols report cases of "biliousness" and "biliary migraine" treated by nonsurgical gall tract drainage. The reader, however, is left in some doubt as to the essential nature of "biliousness" and is not advised as to means of recognizing "biliary" migraine. Many will question the truth of the author's assumption that migraine is a disease of the liver, and will ask whether the clinical improvement noted in the migraine group in cases in which this method of treatment was used may not have been achieved largely by other therapeutic measures.

Dr. W. F. Manges contributes an excellent chapter on roentgen-ray diagnosis of gallbladder disease.

Dr. Lyon's volume may well be considered an authoritative exposition of the case for medical bile tract drainage and will prove of interest and value to the considerable number of physicians now using the method with a view of determining its ultimate value.

THE THERAPEUTIC USE OF DIGITALIS. G. Canby Robinson, Professor of Medicine, Vanderbilt University. Baltimore. Price, $2.50. Pp. 144. Williams and Wilkins Co.

This is the first of a series of "Medicine Monographs"; the original appeared in *Medicine*.

The author states in the preface: "In reviewing the extensive literature on the drugs of the digitalis group the writer has endeavored to keep constantly in mind the needs of the physician who is faced with the problems of the treatment of heart disease. . . In discussing the source of digitalis he calls attention to the value of American-grown digitalis which is equal in activity to that grown in Europe. In discussing biologic essays he favors the cat unit. The potency and permanency of digitalis preparations are reviewed in detail. A chapter devoted to the toxic effects of digitalis contains much valuable information. The therapeutic effects of digitalis is discussed under four heads: effect on the heart muscle, cardio-inhibitory mechanism, blood vessels and kidneys.

A chapter of twenty-seven pages is devoted to the use of digitalis in heart failure. This is subdivided into disturbed cardiomechanism, heart failure with normal cardiac mechanism, vulvular heart disease and disturbance of the

nervous mechanism. There follows a chapter on digitalis in infectious diseases. The question of dosage — intravenous, subcutaneous, intramuscular and by rectum—is discussed in a concise manner. Reference 163 includes all the more important discussions on digitalis.

There is a distinct need for a book of this character in which the entire subject is presented in a concise manner by a physician who is familiar with both pharmacology and clinical medicine. It can be read or referred to with profit by every practitioner of medicine.

TUBERCLE BACILLUS INFECTION AND TUBERCULOSIS IN MAN AND ANIMALS. ALBERT CALMETTE. Authorized English translation by WILLIAM B. SOPER and GEORGE H. SMITH. 689 pages, 25 plates, 31 figures. Baltimore: Williams & Wilkins Company, 1923.

This is an excellent text on the subject mentioned in the title. It contains detailed reference to the morphology, cultural characters, susceptibility to various agents, the chemical composition, toxins, tissue lesions, and mechanism of host infection of the tubercle bacillus. Tuberculosis of the various tissues and organs is discussed fully. Part two contains details regarding tuberculosis in animals other than man. These chapters discuss the bovine and avian types and also the acid-fast bacilli of cold blooded animals. Part three considers the tissue defense and the diagnosis of tuberculous infection. Part four deals with the natural immunity and immunization against tuberculosis. One chapter of this part considers briefly chemotherapy. The text is especially valuable to those interested in more than clinical tuberculosis. For the latter group, however, there is contained much useful information.

INVESTIGATIONS INTO THE OCCURRENCE AND CLASSIFICATION OF THE HAEMOGLOBINOPHILIC BACTERIA. MARTIN KRISTENSEN. Copenhagen: Levin & Monksgaard, 1922.

This report of 272 pages and three plates concerns a review of the causal relationship of *B. influenzae* with the recent and the 1889-1892 pandemics of influenza. To this are added cultural and morphologic studies of *B. influenzae* by the author, as well as summaries of these features by others. It is reasonable to conclude, writes the author, that *B. influenzae* is not the primary influenza microbe. The morphologic and cultural characteristics of *B. influenzae* are given in detail. A comparison of *B. influenzae* with other hæmoglobinophilic bacteria is given. The text, therefore, appeals particularly to those interested in bacteriology.

INFECTION AND RESISTANCE. HANS ZINSSER. Third edition, revised. 666 pages. New York: The MacMillan Company, 1923.

Zinsser's "Infection and Resistance" as a text needs no introduction to workers in immunity and the closely related medical sciences. The third edition, thoroughly revised, contains complete accounts of immunity processes, with added interpretations which recent work in colloidal chemistry are making possible. This text is invaluable to those interested in any phase of immunity, present or past.